State of Hawaii
Department of Health
Communicable Disease Division

Communicable Disease Reports

Bioterrorism Related Diseases

September 26, 2001

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Dear Health Care Provider,

For the Past six months the Communicable Disease Division staff has been developing an in-house training manual for infectious disease emergencies. The entire manual is not scheduled for completion until December 2001. A section of this manual is dedicated to the description of bioterrorism related diseases.

Because of the terrorist attacks of September 11, 2001 in New York, Washington, D.C., and Pennsylvania, the Communicable Disease Division has decided to make available advanced copies of this section of the manual on bioterrorism related diseases to interested healthcare professionals in the community.

This section is a compilation of data from authoritative sources such as the Working Group on Civilian Biodefense series in the Journal of the American Medical Association, the Center for Disease Control and Prevention, the U. S. Army Medical research Institute of Infectious Disease, the American Academy of Pediatrics Red Book, and the American Public Health Association.

The educational material is made available in part from the Centers for Disease Control and Prevention Bioterrorism Preparedness and Readiness Assessment Cooperative Agreement #U90/CCU916969-03.

Sincerely,

Philip Bruno, D.O., F.A.C.P
Chief, Communicable Disease Division

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Chapter 1

Biological Terrorism

Introduction

Biological terrorism (BT) is the deliberate use of disease organisms as weapons against military or civilian populations. Depending on the delivery system, these disease organisms have the potential to kill or incapacitate large numbers of people.

Aerosolization of these microbes is one of the most effective methods of disseminating BT agents into a large population. Biological agents must be milled to a particle size from one to five microns in order to effectively infect the lungs. The aerosols may be delivered by simple technology, including industrial sprayers with nozzles modified to generate the smaller particle size. Other possible routes of exposure include intentional contamination of food and water, and percutaneous exposure.

Potential microbial diseases from an aerosol BT attack are listed in Table 1.1. Most of these diseases are expected to follow a clinical course similar to that of the natural infections, and have limited capacity for person-to-person spread. Pneumonic plague and smallpox are exceptions since they are contagious.

Table 1.1 Bioterrorism Diseases

Anthrax
Botulism
Brucellosis
Plague
Q Fever
Smallpox
Tularemia
Venezuelan Equine Encephalitis
Western Equine Encephalitis
Eastern Equine Encephalitis
Viral Hemorrhagic Fevers

Disease produced following a BT attack will often result in increased morbidity and mortality rates of the exposed population. An article published by the World Health Organization chillingly estimated that 50 kg of aerosolized *Bacillus anthracis* spores dispensed by a line source 2 kilometers upwind of a population center of 500,000 people in ideal meteorological conditions would travel > 20 kilometers downwind, and kill or incapacitate approximately 125,000 people in the path of the biological cloud. A successful BT incident would likely overwhelm the local health care system.

The Federal Bureau of Investigation (FBI) is the lead federal agency for the criminal investigation of BT incidents. All information and specimens related to a BT event are to be preserved as evidence.

Warning Signs

- The clinical or laboratory report of a single case of any disease listed in Table 1.1.
- Large numbers or cases of ill or dead people with similar or unexplained disease or death occurring within hours or days in an other-wise healthy population, especially with fever, respiratory, or gastrointestinal complaints. The sudden appearance of many patients presenting with fever, cough, a fulminant course, and high fatality rate should raise suspicion for anthrax or plague.
- An epidemic curve that rises and falls during a short period of time.
- Lower attack rates among people who remained indoors compared to those outside.
- Clusters of patients from a single locale.
- A disease that is not typical for a given population or age group.
- The identification of an unusual, atypical, or genetically altered microbe.
- Unusual disease transmission through aerosols,

food, or water, which suggests deliberate sabotage with a bio-agent.

➔ A sudden increased incidence of illness, or death, among animals.

➔ Discovery of a potential bioagent delivery system or warnings from the FBI of a credible bioterrorist threat.

Clinical Syndromes

Rapid response to a BT event requires early recognition. Because of the rapid progression of illness and potential for dissemination of some of these agents, it may not be practical to await diagnostic laboratory confirmation. Instead, it will be necessary to initiate a response based on the recognition of high-risk syndromes. The following clinical syndromes should alert healthcare practitioners to the possibility of a bioterrorism related attack.

Inhalational Anthrax: This disease is characterized by a sudden onset of fever, malaise, cough, and chest discomfort followed by severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis within 24-36 hours of onset of illness. Chest x-ray reveals a widened mediastinum.

Botulism: Use of this biological toxin will result in an outbreak of a large number of cases of acute, afebrile, symmetrical descending flaccid paralysis with prominent cranial nerve palsies. The botulinum toxin type may be unusual (e.g. type C, D, F, or G). Patients may share a common geographic location, but without a common dietary exposure. There may be multiple simultaneous outbreaks without a common source.

Brucellosis: People exposed to this organism will present with a systemic febrile illness that may be accompanied by cough, pleuritic chest pain, sacroiliitis, large joint infections, and vertebral osteomyelitis. Genitourinary tract symptoms and hepatitis may occur in some victims. Endocarditis and central nervous system presentations are uncommon. Systemic symptoms may last for weeks or months. Hematologic abnormalities include anemia, neutropenia, and thrombocytopenia.

Pneumonic Plague: This disease presents as an acute, fulminant illness characterized by malaise, high fever, chills, headache, myalgias, cough with the production of bloody sputum, and sepsis. The chest x-ray shows a patchy or consolidated bronchopneumonia. Pneumonic plague progresses rapidly, resulting in dyspnea, stridor, and cyanosis. The terminal course may feature respiratory failure, shock, and ecchymoses. A presumptive diagnosis can be made by identifying a gram-negative coccobacillus with safety-pin bipolar staining organisms in gram-stained or Wright-Giemsa-stained smears from sputum, peripheral blood, lymph node needle aspirate, or other clinical specimens.

Q Fever: The exposure to this organism may result in the sudden appearance of numerous cases of atypical pneumonia syndrome over a few days.

Tularemia: This illness is characterized by sepsis with fever, prostration, and weight loss, but without adenopathy. Respiratory symptoms of substernal discomfort and nonproductive cough may also be present. Chest x-ray may show pneumonitis and pleural effusion. Fever, chills, headache, an ulcerated skin lesion, and regional adenopathy manifest the ulceroglandular form.

Smallpox: Smallpox is manifested by an abrupt onset of malaise, fever, rigors, vomiting, headache, backache, and sometimes delirium followed two or three days later with a generalized synchronous vesiculopustular rash more abundant on the face, extremities, and mucous membranes.

Alphavirus Encephalitis: In a potential BT scenario, alphaviruses should be considered in the differential diagnosis whenever epidemic febrile illness occurs, especially with progression to neurologic disease. Sick or dying equines in the vicinity of an epidemic febrile disease or dying birds should also suggest the possibility of large-scale alphavirus exposure. The general syndrome of alphavirus encephalitis is fever, headache, confusion, obtundation, dysphasia, seizures, paresis, ataxia, myoclonus, and/or cranial nerve palsies.

Viral Hemorrhagic Fever Syndrome: This syndrome is characterized by an acute febrile illness accompanied by malaise, prostration, generalized signs of vascular permeability, and abnormalities of circulatory regulation. Ecchymoses, bleeding at venipuncture sites, epistaxis, and gastrointestinal bleeding are common. There may be conjunctival injection, flushing, mild hypotension, and petechial hemorrhages initially. Generalized mucous membrane hemorrhage and shock with pulmonary, neurologic, hematopoietic, and liver abnormalities follow.

Laboratory Diagnosis

If a case is suspected to be due to bioterrorism, specimen packaging and transport must be coordinated with the State Laboratories Division (SLD) and the Federal Bureau of Investigation. A chain of custody document should accompany the specimen from the

moment of collection. Any questions regarding media and transport should be directed to the SLD Bioterrorism Preparedness Laboratory at (808) 453-6652.

Mass Prophylaxis and Treatment

An intentional biological agent release may produce thousands of casualties. People may die despite the best medical management. Case fatality rates will depend upon the specific microbial agent released and the susceptibility of the exposed population.

The rapid implementation of a mass prophylaxis program is the most effective method of countering the consequences of a biological incident. The best chance to save lives following such an event is through early recognition and prompt administration of appropriate antibiotic therapy and, if available, vaccines to exposed (infected) individuals before symptoms occur.

The bacteria that cause anthrax, plague, tularemia, and brucellosis are susceptible to antibiotics. Antibiotic therapy administered to exposed, or potentially exposed, individuals will prevent or mitigate these diseases and save lives. No preventive antiviral drugs against smallpox currently exist. Botulism is treated with specific antitoxin.

Vaccine supplies for smallpox and anthrax are currently limited. Food and Drug Administration (FDA) approved vaccines against aerosol exposure to plague, brucellosis, and tularemia either do not exist or are ineffective.

Role of the Department of Health

The Department of Health (DOH) has the legal authority to adopt rules requiring and governing immunizations against any communicable disease if a suitable immunizing agent is available for the disease, and a need for immunization against it exists within the State. The DOH may also provide vaccines and other immunizing agents to private and public health care providers for administration to the general public (§325-32, Hawaii Revised Statutes).

The State Epidemiologist will investigate suspected or confirmed outbreaks involving BT organisms (e.g., anthrax, brucellosis, plague, smallpox and tularemia) and other mysterious or undiagnosed disease outbreaks that threaten the public's health. The State Epidemiologist will determine appropriate disease control measures, and report findings and recommendations to the Director of Health.

If a BT event occurs, the DOH will define the distribution and determinants of the disease event, including the case definition, etiology, source, time, person, place, disease pattern, risk factors, exposed populations, and mass prophylaxis recommendations. A mass prophylaxis program will be implemented as soon as possible following a BT incident.

The DOH has established public health nursing standing orders for the administration of antibiotics and vaccines following a BT incident. The Director of Health may order DOH personnel to activate plans for mass prophylaxis and/or immunization when:

- ➔ Single or multiple confirmed or highly suspected cases of a disease listed in Table 1.1 occur within a short period of time, and the source of the infection is unknown.

- ➔ Law enforcement or public health officials have determined that a definite or highly probable release of a virulent biological agent has occurred within the community.

The Public Health Nursing Branch (PHNB) will conduct mass prophylaxis at Public Health Clinics identified and activated by the Director of Health following a BT event. These sites will administer antibiotics and/or vaccines to exposed asymptomatic individuals. Symptomatic or ill individuals will be referred to hospitals or field treatment centers for definitive treatment.

References

1. *Health Aspects of Chemical and Biological Weapons*: Report of a WHO Group of Consultants. Geneva, Switzerland: World Health Organization; 1970:72-99.

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3. Franz DR, Jahrling PB, Friedlander AM, et al: *Clinical Recognition and Management of Patients Exposed to Biological Warfare Agents*. JAMA. 1997, 278: 399-411.

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Table 1.2 Summary of Bioterrorism Incident Mass Prophylaxis Recommendations

Disease	First Choice	Second Choce	Third Choice	Duration
anthrax	ciprofloxacin plus anthrax vaccine	doxycycline plus anthrax vaccine	amoxicillin* plus anthrax vaccine	60 days with antibiotic alone or 30 days with antibiotic plus vaccine
botulism	botulism antitoxin			one (1) dose
brucellosis	doxycycline plus rifampin	trimethoprim-sulfamethoxazole plus rifampin	ofloxacin plus rifampin	3 to 6 weeks
plague	doxycycline	ciprofloxacin	none	7 days
smallpox	vaccinia virus vaccine			one (1) vaccination
tularemia	doxycycline	ciprofloxacin	none	14 days

* Use amoxicillin only if the anthrax strain is proven to be susceptible to penicillin.

Chapter 2

Anthrax

Definition

Anthrax is an acute bacterial zoonotic disease caused by the spore forming gram-positive rod, *Bacillus anthracis.* Aerosolized anthrax spores may be used as a biological warfare or terrorism agent that produces a septic respiratory illness characterized by fever, hypoxemia, cyanosis, dyspnea, shock, and hemorrhagic mediastinitis.

A **widened mediastinum** on chest radiograph in a previously healthy patient with evidence of overwhelming flu-like illness is pathognomonic of advanced inhalational anthrax and should prompt immediate action for search of additional cases (Figure 2.1).

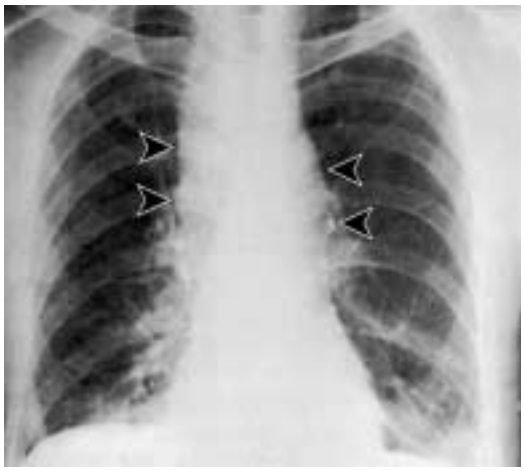

Figure 2.1 Widened mediastinum
(Photo - CDC)

Epidemiology

Anthrax is primarily a disease of herbivores, which acquire infection after coming into contact with soil-borne spores. The incubation period is usually 1 to 7 days with a range of up to 60 days. Person-to-person transmission does not occur. Articles and soil contaminated with spores may remain infective for decades. Assume all exposed individuals are susceptible to infection.

Anthrax occurs worldwide, but is rare in the United States. The last anthrax outbreak in Hawaii was in a herd of dairy cattle in 1938. Humans are infected incidentally when they come into contact with infected animals or animal products.

Reporting Requirements

Hawaii Department of Health (DOH) Administrative Rules, Chapter 156, Communicable Diseases, Exhibits A, B, & C. requires physicians and laboratories to report anthrax cases. Given the rarity of anthrax infection and the possibility that early cases are a harbinger of a larger epidemic, the first suspicion of an anthrax illness must lead to the immediate notification of the DOH.

Disease Investigation Criteria

- Sudden appearance of a large number of patients in the community presenting with an acute febrile flu-like illness and having a high case-fatality rate.
- A single suspected clinical case of anthrax.
- A single case of anthrax in animals.
- Report of a positive laboratory test for *Bacillus anthracis*.

Clinical Syndromes

- **Cutaneous:** A skin lesion evolving during a period of 2-6 days from a papule, through a vesicular stage, to a depressed black eschar that is surrounded by extensive edema. Untreated cutaneous infection may disseminate producing sepsis and meningitis with a case-fatality rate of 5% to 20%. Cutaneous anthrax accounts for 95% of naturally occurring cases.
- **Inhalation (respiratory)**: A brief prodrome

resembling a viral respiratory illness followed by hypoxia, dyspnea, and radiographic evidence of mediastinal widening. The infection produces a hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, and often an hemorrhagic meningitis. Survival is rare. The effect of therapy on symptomatic respiratory anthrax has been marginal, at least in part because early diagnosis is difficult.

- **Intestinal:** Severe abdominal distress followed by fever and septicemia.

- **Oropharyngeal:** Mucosal lesions in the oral cavity or oropharynx, cervical adenopathy, cervical edema, and fever.

- **Meningitis:** Hemorrhagic meningitis occurs in less than 5% of anthrax cases, and may be a complication of any of the above forms of primary anthrax infection.

Laboratory Confirmation

Laboratory confirmation must be pursued in every case with gram stain and culture of appropriate blood and body fluids on routine media under biosafety level 2 conditions. The standard blood culture should show growth in 6 to 24 hours. Because of the potential for drug-resistant strains, including deliberately modified strains, antibiotic-susceptibility testing should be performed on all isolates.

The laboratory must be informed that *B. anthracis* is suspected, so that the isolation of a bacillus from the blood will not be regarded as a contaminant, and that appropriate biochemical testing and colonial morphology review for *B. anthracis* is performed.

Any questions regarding media and transport should be directed to the SLD Bioterrorism Preparedness Laboratory at (808) 453-6652. The SLD can arrange for rapid diagnostic testing of specimens for anthrax bacillus.

Bioterrorism is a Federal Offence. Therefore, all laboratory specimens are considered as evidence. The packaging and transport of bioterrorism suspect specimens must be coordinated with the FBI. A chain of custody document should accompany the specimen from the moment of collection.

Credible Anthrax Threat Protocol

- Call 911 to report the incident to local law enforcement.

- Notify the DOH at (808) 586-4586 during routine business hours or (808) 247-2191 after routine business hours.

- Identify and list all persons potentially exposed.

- Persons potentially exposed to anthrax are not contagious, so quarantine is not appropriate.

- Potentially exposed persons should be advised to await laboratory results of a suspect specimen, and need not be placed on preventive antibiotics. If they become ill before laboratory results are available, they should seek care from their personal physician.

- If the threat of exposure to aerosolized anthrax is credible or confirmed, then persons at risk should begin post-exposure antibiotic prophylaxis and vaccination (if available).

- All first responders should follow local protocols for incidents involving biological hazards. Responders can be protected from anthrax spores by donning splash protection, gloves, and a full face respiratory mask with high-efficiency particle air (HEPA) filters (Level C) or self contained breathing apparatus (SCBA) (Level B).

- Exposed, contaminated persons should be decontaminated with soap and copious amounts of water in a shower. No bleach solutions are required.

- Persons who are to be decontaminated should remove their clothing and personal effects and place all items in plastic bags, which should be labeled clearly with the owner's name, contact telephone number, and inventory of the bag's contents. Personal items may be kept as evidence in a criminal trial or returned to the owner if the threat is unsubstantiated.

- If the suspect envelope or package associated with an anthrax threat remains sealed, then first responders should not take any action other than notifying the police and packaging the evidence. Quarantine, evacuation, decontamination and medicinal prophylaxis efforts are not indicated if the envelope or package remains sealed.

- For incidents involving possibly contaminated letters, the environment in direct contact with the letter or its contents should be decontaminated with a 0.5% hypochlorite solution (a 1:10 dilution of household bleach) following a crime scene investigation. Personal effects may be similarly decontaminated.

Infecton Control measures

Standard barrier precautions are indicated for the duration of illness. Antibiotic therapy sterilizes anthrax skin lesion within 24 hours, but the lesion progresses through its typical cycle of ulceration, sloughing and resolution.

Dressings with drainage from the lesions should be incinerated, autoclaved, or otherwise disposed of as biohazardous waste. Autoclaving and incineration are acceptable procedures for the decontamination of laboratory materials. Spores require steam sterilization, autoclaving, or burning to ensure complete destruction. Hypochlorite is sporicidal and acceptable for environmental cleanup.

Quarantine is not indicated. Immunization of contacts to exposed individuals is not indicated.

Bioterrorism Incident Management

Anthrax Vaccine: BioPort Corporation, 3500 N. Martin Luther King , Jr. Boulevard, Lansing MI 48909, manufactures the only human anthrax vaccine in current use in the U.S. It is a sterile cell free filtrate of cultures from an avirulent nonencapsulated anthrax strain.

Evidence indicates that the vaccine is effective in preventing cutaneous and inhalational anthrax. This vaccine has protected nonhuman primates from experimental respiratory exposure, and was field-tested in employees of four different textile mills in the U.S. The vaccine had an effectiveness of 92.5%.

The routine pre-exposure anthrax vaccine schedule is 0.5 ml administered subcutaneously at 0, 2, and 4 weeks; and then at 6, 12, and 18 months. Pre-exposure anthrax vaccination is currently recommended only for active duty U.S. military personnel or for persons with occupations at high risk of exposure to aerosolized anthrax spores or anthrax-infected animals.

Vaccine supplies are limited and will probably not be available for widespread immunization of civilians if a bioterrorism attack occurs. If an adequate supply of vaccine for civilian use becomes available, administration of vaccine will be determined by a priority list and the quantity of available vaccine. Essential personnel and exposed individuals will receive the vaccine first, followed by the general population, if indicated.

Post-exposure Vaccination: Vaccination with an anthrax vaccine is indicated for individuals exposed to aerosolized *B. anthracis* spores following a bioterrorism event to protect against retained spores within the respiratory tract that are not affected by antibiotics. Previously unvaccinated people will receive three doses of 0.5 ml of vaccine subcutaneously at 0, 2, and 4 weeks.

Those previously vaccinated with fewer than 3 doses will receive a single 0.5 ml booster subcutaneously. Vaccination is not necessary for individuals who have previously received the initial 3 doses of vaccine within the previous 6 months.

Contraindications: Do not administer anthrax vaccine if the patient has a history of hypersensitivity to the vaccine or its components or had a previous history of anthrax infection.

Precautions: Patients who may be pregnant or exhibiting moderate or severe acute illness.

Adverse Reactions: Some patients may exhibit 1) local pain, pruritis, nodules, or inflammation at the injection site, 2) malaise, chills, fever, and lassitude, 3) myalgia, nausea, arthralgia, headache, and 4) anaphylaxis (rare) following anthrax vaccination.

Adverse events occurring after administration of anthrax vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS). VAERS forms can be obtained by calling 800-822-7967. VAERS information is available at http://www.vaers.org.

Antibiotics: *See Table 2.1 and Table 2.2*

Refferences

1. Lew D.P. *Bacillus anthracis (Anthrax)* in Mandell, Douglas, and Bennet's Principles and Practice of Infectious Diseases (2000, fifth edition). Chapter 196. Pages 2215-2220.

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TABLE 2.1 MEDICAL THERAPY FOR PATIENTS WITH CLINICALLY EVIDENT ANTHRAX INFECTION IN AN *ISOLATED* OR *CONTAINED CASUALTY SETTING*

PATIENT CATEGORY	INITIAL THERAPY*	ALTERNATIVE THERAPYΦ	DURATION††
Adult	**ciprofloxacin:** 400 mg intravenously (IV) every 12 hours	**penicillin G:** 4 million units IV every 4 hours; **or** **doxycycline:** 100 mg IV every 12 hours†	60 days
Child§	**ciprofloxacin**: 20 - 30 mg/kg per day IV divided into 2 daily doses, **not to exceed** 1 gram/day	**age < 12 years**: **penicillin G**: 50,000 units/kg IV every 6 hours: or **age > 12 years**: **penicllin G**: 4 million units IV every 4 hours	60 days
Pregnant Women‡	**same** as non-pregnant women	**same** as non-pregnant women	60 days

*Ciprofloxacin is the treatment of choice for anthrax post-exposure prophylaxis during a bioterrorism incident for adults, children, and pregnant women. If ciprofloxacin is contraindicated, then doxycycline is the alternate choice. Extended treatment is needed for total pulmonary clearance of spores, which are not affected by the presence of antibiotics. In vitro studies suggest ofloxacin 400 mg every 12 hours, or levofloxacin 500 mg every 24 hours could be substituted for ciprofloxacin. In the isolated or contained casualty setting, oral antibiotics should be substituted for IV antibiotics as soon as clinical condition improves.

Φ Do not use penicillin until antibiotic susceptibility tests confirm that the anthrax strain is susceptible to penicillin. Use either ciprofloxacin or doxycycline until antibiotic susceptibility test results are known.

† *In vitro* studies suggest tetracycline could be substituted for doxycycline.

§ Doxycycline could also be used in children during an anthrax attack if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic reaction preclude use of penicillin and ciprofloxacin. For children heavier than 45 kg, use adult dosage. For children < 45 kg, use 2.5 mg/kg doxycycline intravenously every 12 hours.

‡ Balancing risks of an anthrax infection with those of antibiotic use in pregnancy, it is recommended to use the above listed agents until antibiotic susceptibility results confirm penicillin sensitivity of the anthrax strain

†† If a person has received 3 doses of anthrax vaccine, then the total duration of antibiotic prophylaxis can be reduced to 30 days.

Adapated from: Inglesby TV, Henderson DA, Bartlett JG, et. al. *Anthrax as a biological weapon: Medical and public health management*. JAMA. 1999, 281: 1735-1745.

TABLE 2.2 MEDICAL THERAPY FOR PATIENTS WITH CLINICALLY EVIDENT ANTHRAX INFECTION IN THE *MASS CASUALTY SETTING* OR FOR *POST-EXPOSURE PROPHYLAXIS*

PATIENT CATEGORY	INITIAL THERAPY*	ALTERNATIVE THERAPYΦ	DURATION††
Adult	**ciprofloxacin:** 500 mg by mouth every 12 hours	**amoxicillin:** 500 mg every 8 hours; **or** **doxycycline:** 100 mg by mouth every 12 hours†	60 days
Child§	**ciprofloxacin**: 10 - 15 mg/kg by mouth every 12 hours, **not to exceed** 1 gram/day	**weight ≥ 20 kg**: **amoxicillin**: 500 mg by mouth every 8 hours: **or** **weight ≤ 20 kg**: **amoxicillin**: 15 mg/kg by mouth every 8 hours; **or doxycycline§**	60 days
Pregnant Women‡	**ciprofloxacin:** 500 mg by mouth every 12 hours	**amoxicillin:** 500 mg by mouth every 8 hours	60 days

* Ciprofloxacin is the treatment of choice for anthrax post-exposure prophylaxis during a bioterrorism incident for adults, children, and pregnant women. If ciprofloxacin is contraindicated, then doxycycline is the alternate choice. Extended treatment is needed for total pulmonary clearance of spores, which are not affected by the presence of antibiotics. *In vitro* studies suggest ofloxacin 400 mg every 12 hours, or levofloxacin 500 mg every 24 hours could be substituted for ciprofloxacin. In the isolated or contained casualty setting, oral antibiotics should be substituted for IV antibiotics as soon as clinical condition improves.

Φ Do not use amoxicillin until antibiotic susceptibility tests confirm that the anthrax strain is susceptible to penicillin. Use either ciprofloxacin or doxycycline until antibiotic susceptibility test results are known.

† *In vitro* studies suggest tetracycline could be substituted for doxycycline.

§ Doxycycline could also be used in children during an anthrax attack if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic reaction preclude use of penicillin and ciprofloxacin. For children heavier than 45 kg, use adult dosage. For children < 45 kg, use 2.5 mg/kg doxycycline intravenously every 12 hours.

‡ Balancing risks of an anthrax infection with those of antibiotic use in pregnancy, it is recommended to use the above listed agents until antibiotic susceptibility results confirm penicillin sensitivity of the anthrax strain

†† If a person has received 3 doses of anthrax vaccine, then the total duration of antibiotic prophylaxis can be reduced to 30 days.

Adapted from: Inglesby TV, Henderson DA, Bartlett JG, et. al. *Anthrax as a biological weapon: Medical and public health management.* JAMA. 1999, 281: 1735-1745.

Chapter 3

Botulism

Definition

Botulism is an acute, afebrile, symmetrical descending flaccid paralysis due to the poisoning of the peripheral neuromuscular junctions and autonomic synapses by a neurotoxin produced from *Clostridium botulinum, C. baratii, or C. butyricum.* Most cases are due to *C. botulinum.*

Biology

C. botulinum is a large, gram-positive anaerobic spore-forming bacillus that is found throughout the world in the soil and marine sediment. The microbe is capable of producing a neurotoxin that is the most poisonous substance known. A single strain usually produces only one type of toxin. There are 7 distinct antigenic toxin types, identified as A, B, C, D, E, F, and G. Types A, B, E, and F produce human disease, whereas types C and D are almost exclusively confined to animals. Type G has not been associated with naturally acquired botulism.

The neurotoxin is a heat-labile, zinc-dependant metalloproteinase. The neurotoxin is usually absorbed into the human bloodstream through the duodenum and jejunum mucosa following the ingestion of food tainted with *C. botulinum*. The neurotoxin can also enter the bloodstream from wounds infected with *C. botulinum.* Three known cases of aerosolized neurotoxin absorbed through the lungs of laboratory workers have been reported. The neurotoxin does not penetrate intact skin.

The neurotoxin binds to the terminal portion of the nerve cell membrane at the neuromuscular junction or autonomic nerve cell synapse, and enters the cell through endocytosis. The neurotoxins cleave the fusion proteins responsible for the release of intracellular vesicles containing acetylcholine. The release of acetylcholine into the synaptic cleft is prevented. This produces a peripheral parasympathetic cholinergic blockade and flaccid muscle paralysis.

The poisoned synapse is rendered permanently useless. New presynaptic axons develop over weeks to months to form new synapses, and allow muscle function to recover.

Epidemiology

There are about 200 cases of human botulism reported in the United States each year. **Botulism is a medical and public health emergency!**

There are five clinical forms of botulism:

- ➔ Foodborne botulism.
- ➔ Infant botulism.
- ➔ Wound botulism.
- ➔ Inhalation botulism.
- ➔ Botulism of undetermined etiology.

In the United States, *C. botulinum* toxin A cases are found predominantly west of the Mississippi River, and toxin B cases are found predominantly in the eastern states. Type E toxin is associated with fish products.

Botulism is NOT a Transmissible Disease and is not spread from person-to-person.

Disease Investigation Criteria

Any case of suspected or proven botulism must be immediately reported to the Department of Health. All suspect or proven cases will be investigated.

Cardinal Signs of Botulism

Patients will exhibit:

- ➔ Normal body temperature.
- ➔ A clear sensorium.

- ➔ Symmetrical neurologic signs.
- ➔ No sensory deficits (except blurred vision).
- ➔ Bilateral cranial nerve palsies occur first: The "4Ds": (diplopia, dysarthria, dysphonia, and dysphagia).
- ➔ Symmetrical descending flaccid paralysis which can affect the respiratory muscles.
- ➔ Normal or slow heart rate in the absence of hypotension.

Foodborne Botulism

Foodborne botulism is transmitted by foods that are not heated or not heated thoroughly before eating, and have a pH > 4.6. Cases are most frequently recognized in outbreaks.

Home canned vegetables, fruits, and fish products are common sources of botulism food poisoning.

Commercial foods and restaurants are still occasional sources for an outbreak of botulism food poisoning.

The incubation period for foodborne botulism is 2 hours to 8 days, but usually occurs 12-36 hours after ingestion of the tainted food or drink.

Initial symptoms are dry mouth, nausea, diarrhea, abdominal cramps, and vomiting.

Evidence of cranial nerve involvement can start with pupillary dilation and blurred vision. There is difficulty seeing, speaking, and swallowing. Cranial nerve abnormalities include: ptosis, gaze paresis, diplopia, nystagmus, dysphagia, dysarthria, facial palsy, diminished gag reflex, tongue weakness, and dysphonia.

Weakness then spreads to the upper extremities, trunk, and lower extremities.

Respiratory failure can result from upper airway obstruction due to pharyngeal muscle weakness and retained secretions, and from diaphragmatic muscle weakness.

Deep tendon reflexes are decreased or absent.

Autonomic dysfunction symptoms include constipation, heart rate abnormalities, loss of responsiveness to hypotension or postural change, hypothermia and urinary retention.

Infant Botulism

Infant botulism is the most common form of botulism currently occurring in the United States. It has been attributed to feeding honey to infants, and in some cases via soil ingestion. Toxins A, B, or F are usually implicated.

The clinical features can include constipation, feeding difficulties, hypotonia, drooling, a weak cry, cranial neuropathies, upper airway obstruction, and respiratory failure.

Wound Botulism

Wound botulism results from soil containing *C. botulinum* spores contaminating an open wound. Toxins A or B are usually implicated. The incubation period is 4 to 14 days.

The cardinal signs of botulism are present. Gastrointestinal symptoms are usually not present. Fever reflects wound infection rather than botulinum intoxication.

Inhalational Botulism

Inhalational botulism is rare and only reported in laboratory workers exposed to accidental aerosolized botulinum toxin in an occupational setting. Inhalational botulism is a major bioweapon threat. A single gram of crystalline toxin evenly dispersed and inhaled would kill more than one million people, although technical factors would make such an ideal dissemination difficult. It is estimated that a point-source aerosol release of botulinum toxin could incapacitate or kill 10% of persons within 0.5 km downwind. Terrorist use of botulinum toxin might also be manifested as deliberate contamination of food.

The three human cases of inhalational botulism demonstrated that symptoms began three days after exposure to a small dose of toxin. Increased mucus in the throat, difficulty swallowing, and dizziness were the first reported symptoms. On the 4th day the cases had restricted eye movement, pupillary dilation and nystagmus, indistinct speech, unsteady gait, and extreme weakness.

The symptoms and signs following an intentional aerosol release of botulism toxin would be expected to resemble the neurologic features of naturally occurring botulism cases.

Biological Terrorism Warning Signs

- Outbreak of a large number of cases of acute flaccid paralysis with cranial nerve palsies.
- Outbreak with an unusual botulinum toxin type (e.g. type C, D, F, or G).
- A common geographic factor among cases, but no common dietary exposure.
- Multiple simultaneous outbreaks with no common source

Diagnosis

Diagnosis and treatment decisions are based upon the history, physical, and neurologic examination. Therapy should not await laboratory confirmation.

Early diagnosis requires clinical suspicion which should result in reduced patient mortality and faster public health response.

Confirmatory laboratory diagnosis is available from the Centers for Disease Control and Prevention (CDC). The Department of Health State Laboratories Division should be consulted for advice on collection, processing, and referral of the specimen to the CDC to perform tests for botulinum toxin.

Specimen Collection Procedure:

- Collect 30 ml (adult) of serum in a red top tube. In addition, collect samples of stool, gastric aspirate, vomitus, and suspected food.
- List the patient's medications (some drugs are toxic to the live mouse assay).
- Keep all samples refrigerated after collection.

The mouse bioassay is the standard laboratory diagnostic test for food and clinical specimens. Type specific antitoxin protects mice against the botulinum toxin present in the sample.

Fecal and gastric specimens are also collected anaerobically and cultured for *C. botulinum*. Toxin production by the isolates is confirmed by the mouse bioassay.

Electromyography may reveal that high rates (20 Hz to 50 Hz) of repetitive nerve stimulation produces a small increment in the motor response. The amplitude of muscle action potentials is reduced, but there is normal nerve conduction velocity, and normal sensory nerve function.

The cerebrospinal fluid examination is normal.

Treatment

Passive immunization with equine antitoxin is the treatment of choice for botulism.

Botulinum antitoxin is available through the Hawaii Department of Health from the CDC.

Always consult the most recent package insert for dosage recommendations.

The licensed antitoxin has a 9% to 20 % incidence of hypersensitivity reactions: urticaria, serum sickness, and anaphylaxis.

Antitoxin administration should always be preceded by a screening skin test for hypersensitivity to the product. If the skin test is positive, cautious desensitization can be accomplished by following the schedule and safety precautions in the package insert.

The U.S. Army has an investigational heptavalent (A, B, C, D, E, F, G) antitoxin.

The Infant Botulism Prevention Program, California State Department of Health Services [(510) 540-2646] has Human Botulism Immune Globulin Intravenous, but it is not available outside of clinical trials.

Supportive care includes*:*

- Fluids and electrolytes.
- Adequate nutrition.
- Oxygen and respiratory therapy.
- Mechanical ventilation.
- Treatment of complications.
- Prevention and treatment of secondary infections.
- Debridement of wounds and drainage of abscesses.
- Avoidance of aminoglycosides and clindamycin which can exacerbate neuromuscular blockade.

Prevention

Closely monitor persons exposed to botulinum toxin, and treat them promptly with antitoxin at the first signs of illness.

An investigational pentavalent (A, B, C, D, E) botulinum toxoid is available through the CDC for laboratory workers.

Mass immunization of civilians with botulinum toxoid is neither feasible nor recommended.

Infection Control

Use Standard Precautions.

Isolation is not indicated.

Botulism is NOT a communicable disease.

Botulinum toxin is easily destroyed. It is heat-labile. Heating to an internal temperature of 85° C for at least 5 minutes will detoxify contaminated food or drink.

Extremes of environmental temperature and humidity will degrade any deliberately released aerosolized toxin, and fine aerosols will eventually dissipate into the atmosphere. Substantial inactivation of aerosolized toxin occurs by 2 days after aerosolization. The decay rate is 1% to 4% per minute.

After exposure to botulinum toxin, clothing and skin should be washed with soap and water. Contaminated surface environmental objects can be cleaned with 0.1% hypochlorite bleach solution if they cannot be avoided for the hours or days required for natural degradation of the botulinum toxin.

References

1. Arnon SS, Schechter R, Inglesby TV, et al. *Botulinum Toxin as a Biological Weapon. Medical and Public Health Management.* JAMA.2001; 285: 1059-1070.

2. Bleck T. *Clostridium Botulinum (Botulism)*. In: Mandell GL, Bennett JE, Dolin R., (eds) Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 5th Edition, Philadelphia: Churchill Livingstone; 2000; 2543-2548.

Chapter 4

Brucellosis

Definition

Brucellosis is a zoonoses caused by four brucella species that occurs in humans following contact with infected animal tissues or ingestion of contaminated raw meat or dairy products. The bacteria are highly contagious by aerosol and commonly cause infections in laboratory workers. Brucellae can be weaponized and released as an aerosol in a building, a battlefield, or a metropolitan area. Therefore, bioterrorism must be considered when an outbreak of brucellosis is reported.

Brucellae are small, aerobic, slow-growing, gram-negative coccobacilli. They do not produce toxins or form spores. *Brucella melitensis* usually infects goats, *Brucella suis* infects swine, *Brucella abortus* infects cattle, and *Brucella canis* infects dogs. Brucellae produce infertility and abortion in their animal hosts.

Epidemiology

Occurrence is worldwide. Brucellosis occurs rarely in Hawaii and is associated with feral swine. From 1996 through the first quarter of 2001, there have been ten cases of brucellosis reported from the Kona coast of the Island of Hawaii. All brucella isolates have been *B. suis*. All cases have had some kind of exposure to feral swine, (i.e., hunting, capture and rearing the swine in backyards, slaughter, or handling the pork).

Brucellosis is predominantly an occupational disease of those working with infected animals or their tissues, (i.e., farm workers, veterinarians, and abattoir workers).

Sporadic cases and outbreaks occur among consumers of raw milk and milk products, especially unpasteurized soft cheese from cows, sheep, and goats.

Reservoirs include cattle, swine, goats, sheep, and occasionally caribou, elk, bison, deer, coyotes, and dogs.

Transmission of infection occurs through contact with infected animals or their tissues including blood and body fluids, aborted fetuses, placentas, and ingestion of raw milk and dairy products (unpasteurized cheese) from infected animals. Airborne infection of animals occurs in pens and stables, and of humans in laboratories and abattoirs.

Incubation Period: 5-60 days.

Brucellosis is not communicable from person-to-person.

Disease Investigation Criteria

- ➔ A single suspected or confirmed case of human brucellosis.
- ➔ A report of brucellosis in animals.
- ➔ Report of a positive laboratory test for brucellosis.
- ➔ The sudden appearance of many previously healthy patients presenting with an unexplained protracted systemic febrile illness.
- ➔ Presentation may include atypical pneumonia, sacroiliitis, large joint infections, vertebral osteomyelitis, orchitis, epididymitis, granulomatous hepatitis, ileitis, colitis, and rarely meningitis or endocarditis.

Clinical Features

Brucellosis is an acute or chronic febrile systemic illness that may have chronic localized infections particularly involving the reticuloendothelial system.

Generalized symptoms may include fever, chills, night sweats, headache, myalgia, arthralgia, back pain, fatigue, and generalized weakness. Cough and pleuritic chest pain are common.

The chest x-ray may be normal or show hilar lymphadenopathy, bronchopneumonia, lung abscesses, and pleural effusions. Hematologic abnormalities may include anemia, neutropenia, and thrombocytopenia.

Syndromes

- Fever of unknown origin.
- Granulomatous hepatitis, ileitis, or colitis.
- Arthritis.
- Vertebral osteomyelitis.
- Sacroiliitis.
- Epididymitis and orchitis.
- Meningoencephalitis.
- Endocarditis.

Diagnosis

- Isolation of *Brucella sp*. from a clinical specimen, **or**
- Fourfold or greater rise in *Brucella sp*. agglutination titer between acute- and convalescent phase serum specimens obtained > 2 weeks apart and studied at the same laboratory, **or**
- Demonstration by immunofluorescence of *Brucella sp*. in a clinical specimen.

Laboratory Confirmation

Laboratory confirmation of brucellosis is usually accomplished by serology. All cases should have arrangements made for acute and convalescent serology to be performed. The serum agglutination test will detect both IgM and IgG antibodies. A titer of 1:160 or greater is indicative of active disease. The IgM titer can be measured by adding 2-mercaptoethanol to the serum. This will destroy the ability of IgM to agglutinate, allowing the IgM titer to be measured by subtracting the now lower titer from the total serum agglutinin titer.

Blood and bone marrow culture during the acute febrile phase of the illness will yield a positive rate of 15% - 70% and 92% respectively. Culture of focal sites of infection may also be positive. The organism grows slowly. Cultures must be kept for at least 6 weeks with periodic blind sub-culturing onto enriched agar plates. A special biphasic culture technique (Castaneda bottle), if available, may facilitate *Brucella sp*. isolation. The organism requires processing under biosafety level 3 conditions.

Antigen detection on DNA extracted from blood mononuclear cells has been accomplished using PCR analysis of a targeted sequence on the 31-kilodalton *B. abortus* protein BCSP 31. This test has been proven to be rapid and specific and may replace blood culture of the organism in the future. PCR for *brucella* species is not available at this time except in research laboratories, but shows promise for future use.

If the case is suspected to be due to bioterrorism, specimen packaging and transport must be coordinated with the State Laboratories Division (SLD) and the Federal Bureau of Investigation. A chain of custody document should accompany the specimen from the moment of collection. Any questions regarding media and transport should be directed to the SLD Bioterrorism Preparedness Laboratory at (808) 453-6652. Rapid diagnostic testing may be available through consultation with the SLD.

Outbreak Control Measures

Standard precautions are adequate, with contact isolation added if draining lesions are present. There is no person- to- person transmission. Environmental decontamination can be accomplished with a 0.5% hypochlorite solution. Quarantine and immunization of contacts is not indicated.

Treatment

See Table 4.1.

Prevention

See Table 4.2.

References

1. APHA. *Brucellosis.* Chin J. (editor), Control of Communicable Diseases Manual. Washington, D.C. American Public Health Association. 2000, 17th edition: 75-78.

2. Franz, DR, Jahrling PB, Friedlander AM, et al. *Clinical Recognition and Management of Patients Exposed to Biological Warfare Agents*. JAMA.1997; 278: 399-411.

3. American Academy of Pediatrics. *Brucellosis*. In: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectious Diseases. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2000: 192-193.

TABLE 4.1 TREATMENT OF BRUCELLOSIS

PATIENT CATEGORY	THERAPY
Adult	**Uncomplicated brucellosis:** Therapy of Choice: **doxycycline** 100 mg orally bid **PLUS rifampin** 600-900 mg orally daily for a minimum of six weeks. **Complicated brucellosis:** For bone and joint infections, endocarditis, and central nervous system disease, long-term therapy with doxycycline and rifampin, plus the addition of 7 to 14 days of an aminoglycoside such as streptomycin or gentamicin is often required. Therapy with doxycycline and rifampin may need to be prolonged for several weeks or months longer than the minimum of 6 weeks depending upon the clinical response. Infectious disease specialty consultation is recommended. **Trimethoprim- sulfamethoxazol**e is an alternative therapy, but relapse rate is up to 30% when used as a single agent. Treatment of endocarditis may require valve replacement. Relapse after appropriate treatment occurs in 5% of cases due to tissue sequestration of organisms from the antibiotics.
Child ≥ 9 Years§	Use adult recommendations.
Child ≤ 9 Years§	**Trimethoprim-sulfamethoxazole** (10/50 mg/kg/day) given in two divided doses daily, **PLUS rifampin** 15 – 20 mg/kg daily in two divided doses for a minimum of 6 weeks. The maximum trimethoprim-sulfamethoxazole dose is 320 mg of trimethoprim per day, and the maximum rifampin dose is 600 mg per day.
Pregnant Women	**Trimethoprim-sulfamethoxazole PLUS rifampin** for 6 weeks.

§ Doxycycline could be used in children younger than 9 years of age during a bioterrorism attack if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic/adverse reaction preclude the use of alternative agents. For children < 45 kg, use 2.0 mg /kg doxycycline every 12 hours. For children > 45 kg use an adult dose. Pediatric use of tetracyclines is associated with adverse effects that must be weighed against the risk of developing a lethal disease.

Adapted from: Franz, D., et al. *Clinical recognition and management of patients exposed to biological warfare agents.* JAMA. August 6, 1997: 399-411.

TABLE 4.2 PREVENTION OF POST-EXPOSURE BRUCELLOSIS

PATIENT CATEGORY	PROPHYLAXIS† ‡
Adult	**Therapy of Choice**: **doxycycline** 100 mg orally bid **PLUS rifampin** 600 orally daily for three to six weeks; **or** **Alternative**: **Ofloxacin** 400mg **PLUS rifampin** 600mg daily for three to six weeks.
Child ≥ 9 Years§ **Child ≤ 9 Years§**	**Use adult regimen.** **Trimethoprim-sulfamethoxazole** 5mg/25 mg /kg every 12 hours daily **PLUS rifampin** 10 mg/kg (maximum 300 mg every 12 hours) for at least 3 weeks to 6 weeks.
Pregnant Women	**Trimethoprim-sulfamethoxazole** 1 (one) DS tablet **PLUS rifampin** 300 mg every 12 hours for at least three to six weeks.
Immunosupressed	Same as for normal adults.

† Prophylaxis for asymptomatic adult patients with confirmed or suspected exposure to brucella species from laboratory exposure, bioterrorism incident exposure, or through inadvertent needlestick injury of live-virus brucella vaccine. All regimens are administered orally.

‡ While evidence for its efficacy has not been proven in clinical trials, it is recommended that persons inadvertently inoculated with strain 19 or Rev-1 vaccines (live attenuated animal vaccines) be given doxycycline 100 mg twice daily, combined with rifampin 600-900 mg once daily for 21 days; for conjunctival inoculations, prophylaxis should be maintained for 4-6 weeks.

§ Doxycycline could be used in children younger than 9 years of age during a bioterrorism attack if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic/adverse reaction preclude the use of alternative agents. For children < 45 kg, use 2.0 mg /kg doxycycline every 12 hours. For children > 45 kg use an adult dose. Pediatric use of tetracyclines and flouroquinolones is associated with adverse effects that must be weighed against the risk of developing a lethal disease.

Adapted from: Franz, D, et. al. *Clinical recognition and management of patients exposed to biological warfare agents.* JAMA. August 6, 1997: 399-411.

Chapter 5

Plague

Definition

Plague is a zoonoses-acquired disease caused by infection with the gram-negative, bipolar-staining bacillus, *Yersinia pestis*.

Acute febrile lymphadenitis (bubonic plague) is the most common clinical presentation. Other presentations include septicemia, pneumonia, and meningitis.

Mortality is high in untreated plague. Early antibiotic treatment reduces mortality.

Aerosolized plague bacillus may be used as a biological weapon to cause an outbreak of primary plague pneumonia (See Figure 5.1). Plague pneumonia has a high fatality rate (57%).

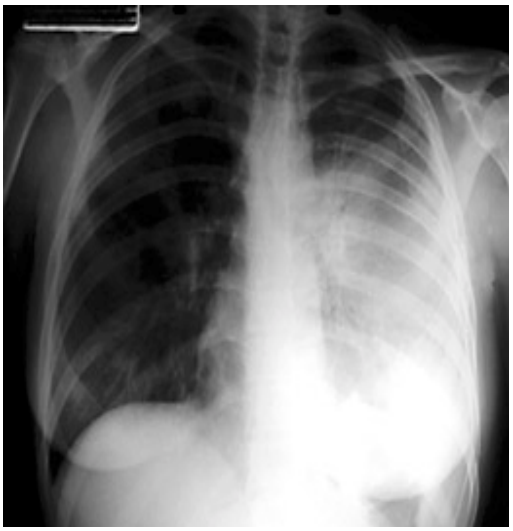

Figure 5.1 Plague lobar pneumonia
(Photo - CDC)

Given the rarity of plague and the possibility that early cases are a harbinger of a larger epidemic, the first suspicion of a case of plague must be immediately reported to the Department of Health (DOH). Hawaii DOH Administrative Rules, Chapter 156, Communicable Diseases, Exhibits A, B, and C, requires physicians and laboratories to report all cases of plague.

Epidemiology

Plague was endemic in Hawaii during the 19th and early 20th century but is now considered to be non-existent. Plague is distributed worldwide. In the United States, about 10 cases per year occur in the southwestern states of New Mexico, Arizona, Colorado, Utah, and California. They usually occur from May to October, when people are outdoors and come into contact with rodents and their fleas.

Rats (*Rattus rattus* and *Rattus norvegicus*), ground squirrels, rock squirrels, and prairie dogs are the important reservoirs. Rabbits, hares, and wild carnivores, as well as domestic cats and dogs, may also be a source of infection to people.

The vector of transmission is a bite from an infected oriental rat flea (*Xenopsylla cheopis*).

Aerosolized respiratory droplets of plague bacillus from humans or household cats with plague pneumonia or pharyngitis, or careless manipulation of *Yersinia pestis* laboratory cultures can, on rare occasion, be the source of an infection.

Hunting, trapping, cat ownership, and rural residence increase risk in endemic areas.

Incubation Period: 2 to 8 days (primary pneumonic plague, 1 to 4 days).

Communicability

- ➔ Bubonic and septicemic plague is usually not contagious unless there is contact with pus from suppurating buboes.
- ➔ Pneumonic plague is **HIGHLY communicable**.
- ➔ Overcrowding facilitates transmission.

➔ No human-to-human transmission has occurred in the U.S. since 1925.

Disease Investigation Criteria

➔ A single suspected or confirmed case of plague.

➔ A single report of plague in an animal.

➔ Report of a positive laboratory test for *Y. pestis.*

➔ The sudden appearance of many patients presenting with fever, cough, a fulminant course and high case-fatality rate should alert a physician to the possibility of anthrax or plague. If cough is primarily accompanied by hemoptysis, the tentative diagnosis is pneumonic plague rather than anthrax.

Clinical Syndromes

Systemic symptoms include fever, chills, headache, malaise, prostration, and leukocytosis.

Bubonic plague has the systemic symptoms plus a painful regional lymphadenopathy ("bubo"). Septicemic plague does not have a bubo, but has fever, hypotension, organ failure, disseminated intravascular coagulation, purpura and digital gangrene.

Pneumonic plague is contagious and rapidly fatal if antibiotic treatment is delayed > 1 day after onset of illness. Fever, cough, hemoptysis, chest pain, and bronchopneumonia are present. Nausea, vomiting, abdominal pain, and diarrhea occurs. A bubo may be present.

Meningitis plague has fever, nuchal rigidity, and usually a bubo. It can complicate any plague syndrome.

Pharyngeal plague has fever, pharyngitis, and cervical adenitis.

Laboratory Diagnosis

Laboratory confirmation of plague is by standard microbiologic culture, but slow growth and misidentification in automated systems may delay diagnosis.

Specimen processing is under ***(BSL-2)*** conditions.

If the case is suspected to be due to bioterrorism, specimen packaging and transport must be coordinated with the State Laboratories Division (SLD) and the Federal Bureau of Investigation. A chain of custody document should accompany the specimen from the moment of collection. Any questions regarding media and transport should be directed to the SLD Bioterrorism Response Laboratory at (808) 453-6652

A presumptive diagnosis can be made microscopically from clinical specimens by identification of the gram-negative coccobacilli exhibiting a characteristic bipolar safety-pin pattern when stained with either Gram or Wayson stains.

Rapid diagnostic tests such as immuno-fluorescence staining, antigen detection, IgM ELISA, and polymerase chain reaction tests can be arranged through the SLD.

Culture of blood, sputum, or bubo aspirate can isolate the plague bacillus within 24 to 48 hours after inoculation on growth media. Most naturally occurring strains of *Y. pestis* produce an F1-antigen in vivo that can be detected in serum samples by immunoassay. A four-fold rise in serum antibody titer, or a single titer of 1:16 or higher is presumptive evidence for plague infection.

Outbreak Control Measures

In naturally acquired infection rid patients, their clothing, and their baggage of fleas using an effective insecticide which is safe for human use.

Hospitalize the patient, if practical.

All hospitalized patients with plague must be placed on droplet precautions for the first 72 hours after the start of effective treatment because of the possibility that pneumonia may supervene. Patients with pneumonic plague may have coughs productive of infectious respiratory droplets. The use of a disposable surgical mask for both the patient, contacts, and providers of care is indicated until 72 hours of antibiotic therapy has been completed. Standard precautions are then adequate for the duration of hospitalization.

In patients with plague pharyngitis or a positive throat culture, droplet isolation should be continued until a negative throat culture has been obtained.

Those who have been in household or face-to-face contact with patients with pneumonic plague, or exposed to aerosolized plague bacillus should be provided chemoprophylaxis and placed under surveillance at home for the development of fever and cough for 7 days.

Those who refuse chemoprophylaxis should be carefully observed for 7 days for the development of fever and cough.

Institute intensive flea control in expanding circles from known foci for epidemics due to natural infection. Implement rodent destruction within affected areas only after satisfactory flea control has been accomplished.

Post-Exposure Decontamination Following a Biological Terrorism Event

A plague aerosol dispersed during a biological attack is estimated to be infectious for about one hour. The aerosol and residual bacilli would be dissipated before plague cases are recognized.

There is no evidence to suggest that residual plague bacilli would pose an environmental threat following a bioterrorism event. The risk for re-aerosolization of *Y. pestis* from the contaminated clothing of exposed persons is low.

Instruct patients to remove contaminated clothing and store in labeled plastic bags; handling clothing minimally to avoid agitation, and to shower thoroughly with soap and water.

Instruct response personnel and health care workers to use standard precautions for infection control purposes and to wear appropriate barriers (e.g. gloves, gown, face shield) when handling contaminated clothing or other contaminated fomites.

Perform environmental surface decontamination using an EPA-registered, facility approved sporicidal/ germicidal agent or 0.5% hypochlorite solution (one part household bleach added to nine parts water).

Bodies of people and carcasses of animals that died of plague should be handled with strict aseptic precautions.

Post-Exposure Prophylaxis

See Table 5.1.

Treatment

See Table 5.2.

References

1. Butler T. *Yersinia Species, Including Plague*, In: Mandell, Douglas, and Bennet's Principles and Practice of Infectious Diseases (2000, fifth edition). Chapter 218. Pages 2406-2414.

2. APHA. *Plague*. Chin J. (editor), Control of Communicable Diseases Manual. Washington, D.C. American Public Health Association. 2000, 17th edition: 381-387.

3. Inglesby TV, Dennis DT, Henderson DA, et al. *Plague as a Biological Weapon: Medical and Public Health Management*. JAMA. 2000; 283: 2281-2290.

TABLE 5.1 PLAGUE POST-EXPOSURE PROPHYLAXIS*

PATIENT CATEGORY	THERAPY
Adult	**doxycycline**: 100 mg orally twice daily for 7 days, **or** **ciprofloxacin**: 500 mg orally twice daily for 7 days.
Child ≥ 9 Years§	**doxycycline**: §, **or** **ciprofloxacin**: 20 mg/kg every 12 hours orally not to exceed 1 gram per day.
Pregnant Women‡	**doxycycline**: 100 mg orally twice daily for 7 days, **or** **ciprofloxacin**:† 500 mg orally twice daily for 7 days.

§ Doxycycline could be used in children during a bioterrorism attack of plague. For children < 45 kg use 2.2 mg/kg orally twice daily with a maximum dose of 200mg/day. For children > 45 kg give adult dose. Pediatric use of tetracyclines and fluoroquinolones may be associated with adverse effects that must be weighed against the risk of developing a lethal disease.

* Prophylaxis is required following face to face contact with a case of pneumonic plague or an aerosol exposure to plague bacillus. Duration of prophylaxis is 7 days.

† Ciprofloxacin may be used in pregnant women and children during, or following a bioterrorism attack due to plague when in the judgement of the attending physician the risk of acquiring or dying from plague is greater than the unknown consequences of the use of ciprofloxacin.

Adapted from: Inglesy, T.V, et al. *Plague as a biological weapon: Medical and public health management.* JAMA. 2000; 283: 2281-90

TABLE 5.2 PLAGUE TREATMENT

PATIENT CATEGORY	THERAPY	
	ISOLATED OR CONTAINED CASUALTY SETTING*	MASS CASUALTY SETTING**
Adult	**PREFERRED CHOICE**: **gentamicin**: 5 mg/kg IM or IV once daily, ***or*** 2 mg/kg loading dose followed by 1.7 mg/kg IM; ***or*** IV 3 times daily† **ALTERNATIVES**: **doxycycline**: 200 mg IV once daily. **ciprofloxacin**: 400 mg IV bid. **chloramphenicol:** One (1) gram IV q6h for 10-14 days is the treatment of choice for plague meningitis, and an alternate treatment for other plague syndromes.††	**doxycycline**: 100 mg orally bid; ***or*** **ciprofloxacin**: 500 mg orally bid
Child§	**PREFERRED CHOICE**: **gentamicin:** 2.5 mg/kg IM or IV 3 times daily† **ALTERNATIVES**: **doxycycline for children > 7 years**.§ **ciprofloxacin:** 15 mg/kg IV twice daily. **chloramphenicol:** 25 mg/kg IV 4 times daily.	**doxycycline** § ***or*** **ciprofloxacin:** 20 mg/kg orally twice daily not to exceed one (1) gram per day
Pregnant Women‡	**PREFERRED CHOICE**: **gentamicin**: 5 mg/kg IM or IV once daily, ***or*** 2 mg/kg loading dose followed by 1.7 mg/kg IM; ***or*** IV 3 times daily† **ALTERNATIVES**: **doxycycline**: 200 mg IV once daily. **ciprofloxacin**: 400 mg IV bid.	**doxycycline**: 100 mg orally bid; ***or*** **ciprofloxacin**: 500 mg orally bid

* One antibiotic should be selected. Therapy should be continued for 10 days. Oral therapy should be substituted when the patient's condition improves. IM indicates intramuscular; IV indicates intravenous.

** Mass casualty implies treatment of hundreds or thousands of patients.

† Gentamicin must be adjusted according to renal function. Neonates up to 1 week of age and premature infants should receive gentamicin, 2.5 mg/kg IV twice daily. In neonates, a gentamicin loading dose of 4 mg/kg should be given initially.

†† Chloramphenicol serum concentrations should be kept between 5 and 20 µg/ml. Concentrations > 25 µg/ml can cause reversible bone marrow suppression.

‡ Ciprofloxacin and doxycycline may be used in pregnant women and children during or following a bioterrorism attack due to plague when in the judgement of the attending physician the risk of acquiring or dying from plague is greater than the unknown consequences of the use of these antibiotics.

§ Doxycyline could be used in children during a bioterrorism attack of plague. For children < 45 kg use 2.0 mg/kg orally twice daily with a maximum dose of 200mg/day. For children > 45 kg give adult dose. Pediatric use of tetracyclines and fluoroquinolones may be associated with adverse effects that must be weighed against the risk of developing a lethal disease. Ciprofloxacin should not exceed 1 gram per day. Chloramphenicol should not exceed > 4 grams per day. Children < 2 years of age should not receive chloramphenicol.

Adapted from Inglesy, T.V., et al. *Plague as a biological weapon: Medical and public health management.* JAMA. 2000; 283: 2281-90

Chapter 6

Smallpox

Definition

Smallpox is an acute systemic viral infection caused by the variola virus, which is clinically manifested by a characteristic generalized centrifugal vesiculopustular rash.

Reporting Requirements

One or more suspected or confirmed cases of smallpox must be immediately reported to the Department of Health, which will trigger a disease outbreak investigation.

Smallpox** is a **Public Health Emergency!

Epidemiology

The last naturally acquired case of smallpox occurred in October of 1977 in Somalia. The World Health Organization certified global eradication in 1980. All known variola virus stocks are held under security at the Centers for Disease Control, Atlanta, Georgia, and at a similar facility in Russia.

There is concern that aerosol release of variola virus could be utilized for bioterrorism. Routine vaccination against smallpox stopped in 1972. The immune status of people vaccinated prior to this date is unknown.

Smallpox is highly contagious and is easily transmitted from person-to-person through droplet nuclei or aerosols expelled from the oropharynx of infected persons. Smallpox can be spread by direct contact, as well as by virus-contaminated clothing or bed linens.

If used as a biological weapon, smallpox represents a serious threat to civilian populations because of its case-fatality rate of > 30% among susceptible persons and the absence of specific therapy.

The secondary attack rate in unvaccinated populations is about 50%. If used in biowarfare, the agent would be disseminated in an aerosol cloud. Large numbers of secondary cases following primary cases from a mass aerosol exposure is anticipated.

Clinical Features

- The incubation period is 7 to 17 days to onset of illness. The illness begins with fever, headache and backache. Abdominal pain and delirium can sometimes occur. This prodrome phase can last 2 to 3 days.

- A maculopapular rash appears 2-4 days after the onset of the prodrome. The rash has a centrifugal distribution and is most dense on the face and extremities. The lesions appear during a 1 to 2 day period and evolve at the same rate, and at any given site the lesions are at the same stage of development. The rash begins on the oropharyngeal mucosa, face and forearms. It then spreads to the trunk and lower extremities. The palms and

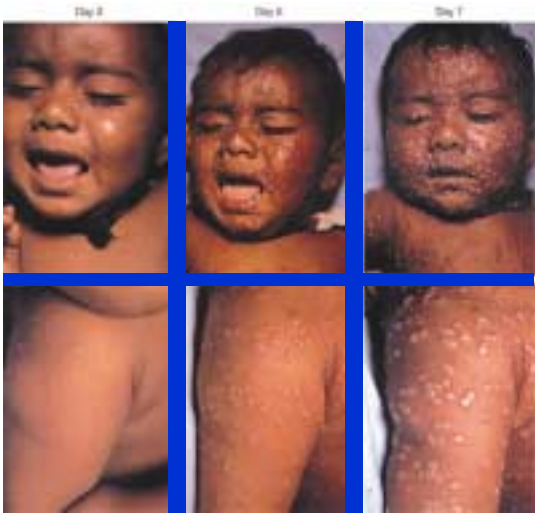

Figure 6.1 Smallpox rash (day 3- 7)
(Photo - CDC)

soles can be involved. Vesicles appear by the 4th or 5th day of the rash, and pustules form by the 7th day (see Figure 6.1). The pustules are round, tense and deeply embedded in the dermis. Scabs appear by day 14 and resolve to leave pitted scars. The patient is communicable from the onset of the skin lesions until separation of all scabs from the skin. The process takes 3 to 4 weeks.

CHICKENPOX (*Varicella*) is the disease that will most often be **confused** with ***SMALLPOX***

- Death usually occurs during the second week of illness from viral toxemia. Encephalitis due to acute perivascular demyelination can complicate the illness.

- Less common, but more severe forms of smallpox include flat-type smallpox and hemorrhagic smallpox. Flat-type smallpox has a mortality rate of > 96% and exhibits severe toxemia and flat, velvety confluent skin lesions that do not progress to form pustules. Hemorrhagic smallpox has a hemorrhagic rash with death occuring in almost all cases 5 to 6 days after the onset of the rash.

- **Chickenpox** (varicella) **is the disease that will most often be confused with smallpox.** Chickenpox lesions appear in crops every few days. The lesions are at different stages of maturation in adjacent areas of the skin. The lesions are superficial and almost never found on the palms and soles. The distribution of the lesions is centripetal, with greater concentration of lesions on the trunk than on the face and extremities. (see Table 6.1)

Laboratory Confirmation

Vaccinated health care workers should obtain potential smallpox specimens using gloves, gown, shoe covers, and a properly fitted N95 mask. Vesicular or pustular fluid can be obtained by opening a skin lesion with the blunt edge of a scalpel, and collecting fluid on a cotton swab. Scabs can be removed with forceps. Specimens should be deposited in a Vacutainer™ tube that should be sealed with adhesive tape at the juncture of stopper and tube. The tube should then be placed into a second durable, watertight container and sent to the State Laboratories Division. Laboratory examination requires high-containment (BSL-4) facilities, therefore, the specimen would most likely be shipped to the CDC for laboratory analysis.

If the case is suspected to be due to bioterrorism, specimen packaging and transport must be coordinated with the State Laboratories Division and the Federal Bureau of Investigation. A chain of custody document should accompany the specimen from the moment of collection. Any questions regarding specimen transport should be directed to the State Laboratories Division Bioterrorism Preparedness Laboratory at (808) 453-6652.

Smallpox infection can be rapidly confirmed in biosafety level 4 laboratories by electron microscopic examination of vesicular or pustular fluid or scabs that demonstrate the brick-shaped virions of variola virus. Definitive laboratory identification and characterization of the virus involves growth of the virus in cell culture or on chorioallantoic egg membrane, and further characterization of the virus strain by use of polymerase chain reaction techniques and restriction fragment length polymorphisms. Once a smallpox case is confirmed, additional cases do not require laboratory confirmation.

Outbreak Control Measures

Vaccinia Virus Vaccine

DryVax® (Wyeth Laboratories, Inc; Marietta, Pennsylvania) is the vaccinia vaccine currently licensed in the United States. It is a lyophilized live virus preparation of infectious vaccinia virus. Vaccinia virus does not contain smallpox (variola) virus.

The administration of vaccinia virus vaccine within the first days after initial exposure to the smallpox virus can reduce symptoms or prevent smallpox disease. Immunity persists for at least 5 years, but can then wane significantly thereafter. Some people can have immunity persist for > 10 years. Antibody levels following a second vaccination dose can remain high for a much longer period, conferring a greater period of immunity that occurs following primary vaccination.

The United States has a reserve supply of freeze-dried vaccinia vaccine sufficient to vaccinate about 15.4 million persons. The small amount of vaccine available and low risk of smallpox bioterrorism attack precludes a pre-exposure preventive vaccination program to protect essential personnel at this time.

A further deterrent to extensive vaccination is the limited quantity of vaccinia immune globulin (VIG).

VIG is recommended for the treatment of severe cutaneous reactions that can complicate vaccination.

The CDC has contracted OraVax (Cambridge, MA) to produce a new smallpox vaccine. The new vaccine will contain live vaccinia virus, but produced in cell cultures by modern vaccine production methods. Forty million doses of the new vaccine will be produced initially, with anticipated delivery of the first full-scale production lots in 2004. The vaccine will be administered with bifurcated needles produced by OraVax. The vaccine will be held in reserve as part of a national stockpile, and released only in the event of a confirmed case of smallpox, or when vaccination against vaccinia virus is warranted.

Vaccination with the DryVax® preparation is performed by cutaneous inoculation of vaccinia virus and scarification using the multiple-puncture technique with a bifurcated needle. The preferred sites for inoculation are the skin over the insertion of the deltoid muscle and the posterior aspect of the arm over the triceps muscle. (see Figure 6.2)

A sterile bifurcated needle is inserted into an ampoule of reconstituted vaccine and on withdrawal, a droplet of vaccine sufficient for vaccination containing an infectious dose of about 2×10^5 plaque forming units of vaccine strain vaccinia virus is held by capillary attraction between the two tines of the needle.

Fifteen perpendicular strokes of the needle are rapidly made in an area of about 5mm in diameter that penetrates into the epidermis of the deltoid region of the arm. The punctures should be vigorous enough that a trace of blood appears at the vaccination site. After vaccination, excess vaccine should be wiped from the site with sterile gauze. The gauze should then be discarded in a hazardous waste receptacle.

Two to five days after primary vaccination, a papule forms and then becomes a vesicle two to three days later. The vesicle reaches a maximum size by day 8 to 10. A scab forms within two weeks leaving behind a scar when healing is complete. Mild fever and localized (regional) swollen lymph glands are often present two weeks after vaccination. Lymphadenopathy can persist for 2 to 4 weeks after the skin lesions have healed. Maximum viral shedding from the vaccination site occurs 4 to 14 days after vaccination, but can persist until the scab separates from the skin. Persons being revaccinated may not develop a blister, and the progression of the lesion at the site of vaccination may be shorter. (see Figure 6.3)

The objectives in caring for a smallpox vaccination site are to avoid spread of virus from the vaccination site to another area of the body such as the eyes, to avoid spread to another person, and to keep the area clean and dry. The site should be kept covered with a non-occlusive bandage until the scab has fallen off and the underlying skin has healed. An occlusive (air-tight) bandage should not be used. The site should be kept dry. Normal bathing or showering can proceed, but the vaccination site should be covered during water exposure with a plastic covering. Do not direct shower water to the vaccinated area. After drying off, replace the plastic cover with a simple non-occlusive bandage. After changing the bandage, or any time the vaccination site is touched, wash hands thoroughly with soap and water. Hand washing is the most important measure to prevent transmission of vaccinia to another person or to another part of the body. Contact with anyone at risk of complications of smallpox vaccination should be avoided until the scab has fallen off.

The overall risks of serious complications of smallpox vaccination are low and occur more frequently in persons receiving their first dose of vaccine and among young children. The most frequent serious complications of vaccination are encephalitis (brain inflammation), vaccinia necrosum (progressive destruction of skin and other tissues at the vaccination site), and eczema vaccinatum (severe and destructive infection of skin affected by eczema or other chronic skin disorder caused by spread of vaccinia virus).

Encephalitis complicates the primary smallpox vaccination in one out of 300,000 doses. Encephalitis occurs in about one in 200,000 doses in persons being re-vaccinated for smallpox. Vaccinia necrosum occurs in persons who have abnormalities of their immune system, for whom the vaccine is contraindicated. Eczema vaccinatum occurs in recipients who have eczema or other chronic skin conditions also for whom the vaccine is contraindicated.

Generalized vaccinia is the development of vaccination lesions away from the vaccination site. This occurs in one in 5,000 primary vaccinations, and one in 110,000 revaccinations. Generalized vaccinia in persons without underlying illness (such as immune deficiency) is generally self-limited and requires little or no therapy.

Accidental transfer of vaccinia from the vaccination site to other parts of the body occurs in one in 1,700 primary vaccinations, and one in 40,000 revaccinations.

Accidental transfer of vaccinia from the vaccination site to other parts of the body can be prevented by hand washing after touching the vaccination site.

On rare occasions, almost always after primary vaccination, vaccinia virus has been reported to cause fetal

infection after vaccination of a pregnant woman. Fewer than 50 instances of fetal vaccinia are known, but cases have been observed as recently as 1978. Fetal vaccinia usually results in stillbirth or death of the infant shortly after delivery. Vaccinia vaccine is not known to cause congenital malformations.

Because the vaccinia virus is present at the vaccination site, other persons can become infected if they come in direct contact with the vaccinee's lesions. Vaccinees can also transfer virus from the vaccination site to another person by touching the lesion and then touching the other person. The exact risk of infection by such routes of transmission is unknown; however, virus can be cultured from the vaccination site until the skin heals. Most instances of contact transmission of vaccinia do not lead to serious illness in the contact. However, about 30% of contact transmission results in eczema vaccinatum.

Contraindications to routine smallpox vaccination include:

- Persons who have ever been diagnosed as having eczema, even if the condition is mild or is not presently active.
- Persons whose household contacts have eczema or a history of eczema.
- Persons with diseases or conditions which cause immunodeficiency, such as HIV infection, leukemia, lymphoma, generalized malignancy, agammaglobulinemia, or persons on therapies with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids.
- Persons whose household contacts have an immunodeficiency disease or are being treated with therapy listed above.
- Persons with other acute or chronic skin conditions, such as atopic dermatitis, burns, impetigo, or varicella zoster (shingles) should not be vaccinated until the condition resolves.
- Women who are pregnant or who are planning to become pregnant within a month following vaccination.
- Persons with serious life-threatening allergies to the antibiotics polymyxin B, streptomycin, tetracycline, or neomycin.

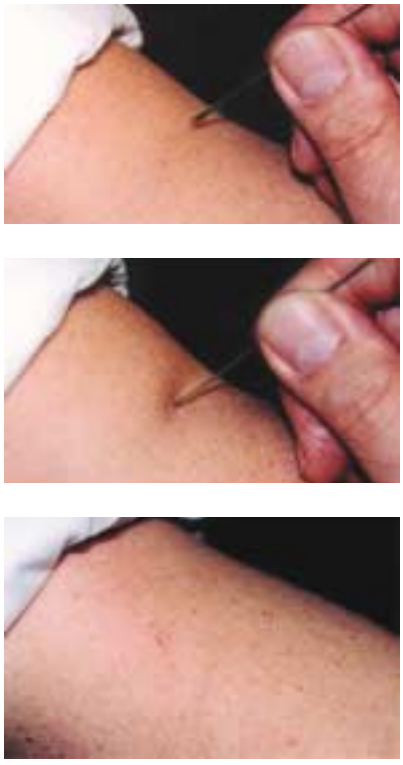

Figure 6.2 Smallpox innoculation.
(Photo - CDC)

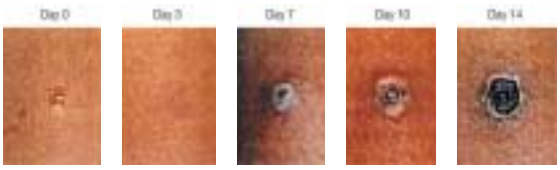

Figure 6.3 Smallpox vaccination site.
(Photo - CDC)

During a smallpox emergency no absolute contraindications exist regarding vaccination of persons with a high-risk exposure to smallpox. Persons at greatest risk for experiencing serious vaccination complications are also at greatest risk for death from smallpox. If a relative contraindication to vaccination exists, the risk for experiencing serious vaccination complications must be weighed against the risk for experiencing a potentially fatal smallpox infection. When the level of exposure risk is undetermined, the decision to vaccinate should be made after prudent assessment by the clinician, and the patient, of the potential risks versus benefits of smallpox vaccination.

Vaccine complications are treated with Vaccinia Immune Globulin (VIG). It is effective in reducing the morbidity and mortality from vaccinia necrosum,

eczema vaccinatum, severe cases of generalized vaccinia, and possibly ocular inoculation. It is of no benefit for the treatment of post-vaccinial encephalitis, and is contraindicated for the treatment of vaccinial keratitis.

The standard VIG dose is 0.6 mL/kg intramuscularly. The total dose for a 70 kg adult would be 42 mL. Therefore, the dose may need to be divided and given over a 24 to 36 hour period. Doses may be repeated, usually at intervals of 2 to 3 days until recovery begins.

VIG and Vaccinia Virus Vaccine are only available to civilians through the CDC (404-639-3670) during business hours, and 404-639-3311 after hours, weekends, and holidays). The CDC bioterrorism response coordination hotline is 404-639-0385.

Bioterrorism Outbreak Control Measures

All suspect smallpox cases should be isolated immediately. All household and other face-to-face contacts should be vaccinated and placed under surveillance. Contacts are defined as persons who have been in the same household as the infected individual, or who have been in face-to-face contact with the patient after the onset of fever. Ensure that all susceptible people identified are informed of their risk of contracting smallpox. Parental/legal guardian permission for vaccination will be required for minors.

The Department of Health must be immediately notified of any suspected or confirmed case of smallpox. The Department will notify the CDC in order to request a supply of smallpox vaccine (i.e. vaccinia virus vaccine) and VIG.

Because the widespread dissemination of smallpox virus by aerosol poses a serious threat in hospitals, patients should be isolated in the home or other non-hospital facility whenever possible. Home care for most people is a reasonable approach, given the fact that little can be done for a patient other than to offer supportive therapy.

In the event of an aerosol release of smallpox and a subsequent outbreak, patients suspected to have smallpox, and people determined to have been at high risk of exposure to the aerosol release should be vaccinated. The rationale for vaccinating individuals suspected of having smallpox is to ensure that some with a mistaken diagnosis are not placed at risk of acquiring smallpox, and that vaccination administered within the first few days after exposure (and perhaps as late as 4 days) may prevent or significantly ameliorate subsequent illness.

An emergency post-exposure vaccination program is indicated for all essential health care workers and essential government personnel.

Those who have been vaccinated at some time in the past will normally exhibit an accelerated immune response. It would be prudent to assign those who had been previously vaccinated to duties involving close patient contact. Because contacts, even if infected, are not contagious until onset of rash, a practical strategy might be to have all contacts check their temperature at least once each day, preferably in the evening. Any increase in temperature higher than 38º C (101º F) during the 17 day period following last exposure to the cases would suggest the possible development of smallpox, and be cause for isolating the patient immediately, preferably at home, until it could be determined that the contact does not have smallpox. All close contacts of patients should be vaccinated.

Uncooperative patients or contacts should be quarantined.

In the outbreak setting, all hospitalized patients and hospital employees should be vaccinated. For immunocompromised individuals or for those whom vaccination is otherwise contraindicated, VIG should be provided, if available. If it is not available, a judgment will have to be made regarding the relative risks of acquiring the disease in contrast to the risks associated with vaccination.

In the event of a limited outbreak with few cases, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air filtration. In larger outbreaks, home isolation and care should be the objective for most patients. Employees for whom vaccination is contraindicated should be furloughed. Personnel involved with direct smallpox patient care activities should observe strict contact and airborne precautions using gloves, gowns, shoe covers, eye shields, and correctly fitted N95 masks for additional protection until post-vaccination immunity has been demonstrated. This immunity occurs 6 to 8 days after vaccination. Contact precautions, including the wearing of shoe covers, should continue after the development of post-vaccination immunity in order to prevent the spread of virus throughout the facility. All laundry and waste should be placed in biohazard bags and autoclaved before being laundered or incinerated. A number of outbreaks in the past have occurred in laundry workers who handled linens and blankets used by patients.

Patients who die of smallpox should be cremated whenever possible. Mortuary workers should be vaccinated.

Post-exposure therapy for smallpox consists of supportive care and antibiotics for superimposed bacterial infection. No antiviral agents have yet proved effective for the treatment of smallpox.

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Table 6.1 Distinguishing Smallpox from Chickenpox

	Smallpox	Chickenpox
Incubation	7 - 17 days	14 - 21 days
Prodrome (illness prior to rash)	2 - 4 days	Minimal to none
Distribution	Lesions initially tend to develop on the face and extremities, progressing to the trunk of the body. Rash also **found** on palms and soles	Lesions initially tend to develop on the trunk of the body, progressing to the face and extremities. Lesions also tend to be more abundant on the trunk than on the face and extremities Rash **rarely found** on palms and soles.
Depth of Rash	Deeply embedded	Superficial
Progression of Rash	Lesions develop and progress at **same rate.**	Lesions **appear successively** and progress at varying rates
Scab Formation	10 - 14 days after onset of rash.	4 - 7 days after rash onset
Scab Separation	14 - 28 days after rash onset	< 14 days after rash onset

Chapter 7

Staphylococcus Enterotoxin B

Definition

Staphylococcal enterotoxin B (SEB) is a protein exotoxin secreted by *S. aureus*. SEB is one of the pyrogenic toxins responsible for the symptoms of staphylococcal food poisoning. SEB has a broad spectrum of biological activity, and causes a different clinical syndrome when inhaled into the respiratory tract. SEB can be mass produced and used as a biological weapon. Aerosolized SEB would be expected to produce significant morbidity in an exposed population. It is estimated that up to 80% or more of exposed military personnel could become clinically ill and unable to perform their mission for 1-2 weeks following exposure to SEB.

Clinical Manifestations

SEB produces an intense inflammatory reaction in the host that injures tissues. This inflammation is mediated through the production of pro-inflammatory cytokines.

Symptoms of SEB intoxication begin after a latent period of 3 to 12 hours after inhalation, or 4 to 10 hours after ingestion.

Symptoms following inhalation of SEB include fever, chills, headache, myalgias, cough, retrosternal chest pain, and dyspnea. Physical examination may demonstrate conjunctival injection, postural hypotension from fluid loss, and possibly bilateral wheezes, crackles or rales on chest auscultation. The lungs develop pulmonary edema secondary to the inflammatory response initiated by the SEB. Chest x-ray is usually normal, but in severe cases show increased interstitial markings, atelectasis, or bilateral pulmonary infiltrates consistent with pulmonary edema. Fever may last for 5 days. Cough may persist for up to four weeks. The person may be incapacitated for 1 to 2 weeks. A complete blood count will reveal a neutrophilic leukocytosis, and the erythrocyte sedimentation rate will be increased. These laboratory results indicate an inflammatory response by the host to the toxin.

SEB food poisoning causes nausea, vomiting, and abdominal cramps. Sometimes diarrhea and fever are present.

Diagnosis

The diagnosis of SEB intoxication is based on clinical and epidemiologic features. Infection due to respiratory tract pathogens and exposure to other inhaled chemicals needs to be excluded. An SEB attack would cause cases to present in large numbers over a very short period of time, probably within a single 24-hour period. SEB intoxication tends to plateau rapidly to a fairly stable clinical state, whereas inhalational anthrax, tularemia, or plague would all continue to progress if left untreated. Tularemia and plague more frequently demonstrate pneumonic infiltrates on the chest radiograph.

Laboratory confirmation of SEB intoxication includes antigen detection by enzyme linked immunosorbent assay (ELISA) on environmental and clinical samples, and gene amplification procedures (polymerase chain reaction) to detect *S. aureus* genes on environmental samples. SEB is transient in the blood, and may not be detectable in serum by the time symptoms occur. The toxin accumulates in urine and can be detected for several hours post exposure. Urine samples should be obtained and tested for SEB. Respiratory secretions and nasal swabs may demonstrate SEB if sampled within 24 hours after exposure. Most patients will develop an antibody response to SEB. Acute and convalescent sera should be drawn to establish a retrospective diagnosis.

Treatment

Treatment consists of general medical supportive care. No specific antidote exists. Attention must be directed to ensure proper oxygenation, ventilation, clearance of pulmonary secretions, and fluid and electrolyte balance. Vasopressors may be needed for hypotension. Diuretics might be needed for pulmonary edema. Acetaminophen may be used to treat fever. Cough suppressants may be needed.

Prevention

No vaccine or medication currently exists for prophylaxis. Experimental vaccines are being evaluated, and vaccination is thought to be the most practical defense. The use of a protective chemical mask is the most practical method of prevention during an SEB attack.

Standard Precautions for health care workers are adequate when caring for persons with SEB intoxication. SEB is not dermally active and secondary aerosols from patients are not a hazard.

Decontamination is with soap and water. Destroy any food that may have been contaminated.

Reference

This chapter has been abstracted from the U.S. Military Medical Research Institute of Infectious Diseases biowarfare course: *Biological Warfare and Terrorism Medical Issues and Response* Student Material Booklet, Satellite Broadcast, September 26-28, 2000. *Staphylococcal Enterotoxin B*. Pages 73-76.

Chapter 8

Tularemia

Definition

Tularemia is an acute bacterial disease of both animals and humans caused by the gram-negative, aerobic, catalase-positive coccobacillus, *Francisella tularensis*.

F. tularensis biovar tularensis (type A) may be highly virulent in humans and animals, produces acid from glycerol, demonstrates citrulline ureidase activity, and is the most common biovar isolated in North America. *F. tularensis* biovar palaearctica (type B) is relatively avirulent, does not produce acid from glycerol, and does not demonstrate citrulline ureidase activity. *F. tularensis* biovar palaearctica (type B) is the strain responsible for most cases of tularemia in Europe and Asia.

Tularemia is considered to be a potential bioterrorism agent, particularly if used as an aerosol. Cases acquired by inhalation would present as a primary pneumonia. Such cases require prompt identification and treatment to prevent a fatal outcome.

Epidemiology

Tularemia occurs in North America, continental Europe, the former Soviet Union, China, and Japan. Arkansas, Missouri, and Oklahoma reported 53% of the total U.S. cases from 1990-1994. South Dakota, Montana, Tennessee, Kansas, Colorado, and Illinois account for the next 22%.

Tularemia occurs most frequently between June and August, and in December. The summer peak corresponds to a greater number of tick-acquired cases, whereas the smaller peak in late winter reflects an increased number of hunting-associated cases.

Tularemia is an occupational hazard for laboratory workers, veterinarians, sheep workers, hunters or trappers, farmers, cooks, and meat handlers.

Reservoir includes rabbits, hares, voles, muskrats, beavers, squirrels and other rodents and hard ticks.

The incubation period is usually 3 to 5 days, with a range of 1 to 14 days. Person to person transmission does not occur. Assume all exposed individuals are susceptible to infection. Long-term immunity follows recovery.

Transmission

- Arthropod bites from the wood tick *Dermacentor andersoni*, the dog tick *Dermacentor variabilis*, the Lone Star tick *Amblyomma americanum*, and the deer fly *Chrysops discalis*.
- Inoculation of skin, conjunctival sac, or oropharyngeal mucosa with contaminated water, blood, or tissue while handling carcasses of infected animals (e.g. skinning, dressing, performing necropsies).
- Handling or ingesting insufficiently cooked meat of infected animals.
- Drinking contaminated water.
- Inhalation of dust from contaminated soil, grain, or hay.
- Rarely, from bites of mammals whose mouths were contaminated from eating an infected animal.
- Contaminated pelts or paws of animals.
- Laboratory accidents.

Person-to-person transmission has never been documented.

Disease Reporting Requirements

The first suspicion of an illness due to tularemia must lead to the immediate notification of the Department of Health (DOH). Hawaii DOH Administrative Rules, Chapter 156, Communicable Diseases, Exhibits A, B, & C requires physicians and laboratories to report tularemia cases.

Disease Investigation Criteria

- A single suspected clinical case of tularemia and all cases of pneumonia due to *F. tularensis.*
- A single case of tularemia in animals.
- Report of a positive laboratory test for *Francisella tularensis*.
- Sudden appearance of a large number of previously healthy young adults with an undiagnosed bacterial pneumonia having a high case-fatality rate.

Clinical Manifestations

Tularemia Syndromes

- **Ulceroglandular** - a skin ulcer with regional lymphadenopathy.
- **Glandular** - regional lymphadenopathy with no cutaneous ulcer.
- **Oculoglandular** - conjunctivitis with preauricular lymphadenopathy.
- **Intestinal** - pharyngitis, abdominal pain, vomiting, and diarrhea.
- **Pneumonic** - primary pleuropulmonary disease.
- **Typhoidal** - febrile illness without early localizing signs and symptoms.

Intentional Aerosol Release

Release of *F. tularensis* in a densely populated area would be expected to result in an abrupt onset of large numbers of cases of acute, nonspecific febrile illness beginning 3 to 5 days after exposure with pleuropneumonitis with hilar adenopathy developing in a significant proportion of cases during the ensuing days and weeks. Without proper treatment the clinical course could progress to respiratory failure, shock, and death.

Until the etiology becomes clear, clinicians would need to work closely with epidemiologists and diagnostic laboratories to differentiate the illness from various community-acquired pneumonias and to determine if it could have resulted from the use of one of several potential bioterrorism weapons agents, such as those causing tularemia, plague, anthrax, or Q fever.

Once a substantial cluster of cases of inhalational tularemia has been identified, epidemiological findings should suggest a bioterrorist event. The abrupt onset and single peak cases would implicate a point-source exposure without secondary transmission. Among exposed persons, the attack rates would likely be similar across sex and age groups, and risk would be related to degree of exposure to the point source.

An outbreak of inhalational tularemia in an urban setting should trigger a high level of suspicion of an intentional event, since all reported cases of inhalational tularemia outbreaks have occurred in rural areas.

Laboratory Confirmation

Francisella tularensis can be cultured from blood and body fluid specimens on cysteine-glucose blood agar or by inoculation of laboratory animals with clinical specimens.

Francisella tularensis isolation from clinical specimens is difficult due to the special growth requirements of the organism, and is also extremely hazardous to laboratory workers. Therefore, diagnosis is usually confirmed serologically by acute and convalescent IgM and IgG agglutination antibody titers. Immunofluorescent antibody testing and polymerase chain reaction testing of sputum and lymph node aspirates and polymerase chain reaction testing of blood are helpful in providing early diagnoses.

A laboratory diagnosis of tularemia can be confirmed by the isolation of *Francisella tularensis* from a clinical specimen, demonstration *of Francisella tularensis* in a clinical specimen by immunofluorescence, or a fourfold or greater rise in agglutination titer between acute and convalescent-phase serum specimens obtained ≥ 2 weeks apart, and analyzed at the same time and in the same laboratory.

Infection Control Measures

Standard precautions are adequate for handling contaminated secretions from eyes or wounds.

Isolation of tularemia patients is not indicated.

Microbiology laboratory personnel should be alerted when tularemia is clinically suspected. Routine diagnostic procedures can be performed in biological safety level 2 (BSL-2) conditions. Examination of cultures in which *F. tularensis* is suspected should be performed in a biological safety cabinet. Manipulation of cultures and other activities involving infectious

materials with a potential for aerosol or droplet production (centrifuging, grinding, vigorous shaking, growing cultures in volume, animal studies) require BSL-3 safety measures.

When *F. tularensis* is presumptively identified in a routine BSL-2 laboratory, the specimen should be referred to a BSL-3 laboratory (e.g. State Laboratories Division) for confirmation and additional testing.

Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to cause aerosols, such as bone sawing, should be avoided.

Clothing or linens contaminated with body fluids of patients infected with *F. tularensis* should be disinfected per standard precautions protocols.

Quarantine and immunization of contacts is not indicated.

Inanimate objects such a laboratory workbench or floor that has been contaminated with material containing *F. tularensis* can be disinfected by cleaning with a ten percent bleach solution followed by further cleaning of the area with a 70% solution of alcohol. Soap and water can be used to flush away less hazardous contaminations.

Persons with direct exposure to powder or liquid aerosols containing *F. tularensis* should wash body surfaces and clothing with soap and water. Standard levels of chlorine in municipal water sources should protect against waterborne infection.

Treatment

In a contained casualty situation following a bioterrorism incident involving tularemia where logistics permit individual medical management the Working Group on Civilian Biodefense recommends parenteral antimicrobial therapy (see Table 8.1)

Streptomycin is the traditional drug of choice to treat tularemia, but this antibiotic is in short supply and difficult to obtain. A more pragmatic and acceptable alternative choice is gentamicin. The duration of therapy is ten days. Gentamicin therapy must be monitored closely, and the dose modified in renal failure patients and in neonates.

Tetracyclines and chloramphenicol are also used to treat tularemia, but relapses and primary treatment failures have been reported with these agents. Therapy should be continued for 14 to 21 days if one of these drugs are used in order to reduce the relapse rate.

Quinolones are promising candidates for the treatment of tularemia. Ciprofloxacin has activity against *F. tularensis in vitro*, and in animals. Ciprofloxacin has been used successfully to treat a limited number of cases of tularemia in both children and adults. The recommended duration of therapy with ciprofloxacin is ten days.

Treatment of tularemia cases in a mass casualty setting includes oral therapy with either ciprofloxacin or doxycycline.

Pregnant women should receive gentamicin for the treatment of tularemia if individual medical management is possible. A short course of gentamicin poses a low risk to the fetus when used to treat tularemia in pregnant women. Rare cases of fetal nerve deafness and renal damage have been reported with other aminoglycosides, but have not been reported with gentamicin. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses. In a mass casualty situation, oral ciprofloxacin is considered the best alternative to gentamicin for pregnant women.

Prevention

Post-exposure prophylaxis in a mass casualty setting following a bioterrorism incident with tularemia is listed in Table 8.2. The oral administration of doxycycline or ciproflocacin for 14 days is recommended for both adults and children. The ciprofloxacin dosage for children should not exceed 1 (one) gram per day. The Working Group on Civilian Biodefense believes the benefits to children from short courses of doxycycline or fluoroquinolones outweigh the risks of their use in this setting.

In a circumstance in which the weapon attack has been covert and the event is discovered only after persons start to become ill, persons potentially exposed should be instructed to begin a fever watch. Persons who develop an otherwise unexplained fever or flu-like illness within 14 days of presumed exposure should begin treatment for tularemia.

In the laboratory, persons who have had potentially infective exposures to *F. tularensis* should be administered oral postexposure antibiotic prophylaxis if the risk of infection is high (e.g. spill, centrifuge accident, or needlestick). If the risk is low, exposed persons can be placed on a fever watch and treated if they develop symptoms.

Postexposure prophylaxis of close contacts of tularemia patients is not recommended because person- to-person transmission of the disease is not known to occur.

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Table 8.1 Treatment of Tularemia

Patient Category	Therapy
Adult	**gentamicin**: 5 mg/kg/d IV in divided doses for 10 days.
Child	**gentamicin**: 3-5 mg/kg/d IV in divided doses for 10 days.
Pregnant Women	same as for adults

TABLE 8.2 POST-EXPOSURE PROPHYLAXIS FOR TULAREMIA

PATIENT CATEGORY	THERAPY
Adult	**doxycyline**: 100 mg orally twice daily for 14 days, ***or*** **tetracycline**: 500 mg orally four times daily for 14 days.
Child§	**doxycycline**: for 14 days §, ***or*** **ciprofloxacin**:† 10-15 mg/kg orally every 12 hours not to exceed 1 gram/day for 14 days.
Pregnant Women†	**ciprofloxacin**:† 500 mg orally twice daily for 14 days.

§ The use of doxycycline in pediatric patients < 7 years of age may be associated with adverse effects. In a bioterrorism incident the use of doxycycline to prevent a potentially lethal disease must be weighed against the potential side effects of the antibiotic. For children < 45 kg use 2.2 mg/kg orally twice daily with a maximum dose of 200 mg/day. For children > 45 kg give the adult dose.

† Use of ciprofloxacin is based on successful use in treating 6 cases in adults. The use of ciprofloxacin in pregnancy or pediatrics is not usually recommended, and the potential benefit in preventing a potentially lethal disease must be weighed against the unknown risk in pregnancy or the pediatric age group. Tetracyclines are contraindicated in pregnancy.

Adapted from: Franz, D., et. al. *Clinical recognition and management of patients exposed to biological warfare agents*. JAMA. August 6, 1997: 399-411.

Chapter 9

Alphavirus Encephalitis

Definition

The alphaviruses are a genus of mosquito-borne neurotropic RNA viruses that belong to the *Togaviridae* family.

There are three antigenic complexes of alphaviruses that cause neurologic disease in the Americas: Venezuelan equine encephalitis (VEE); western equine encephalitis (WEE); and eastern equine encephalitis (EEE). Each complex has several subtypes.

Venezuelan equine encephalitis was tested as a biological weapon during the United States Offensive Weapons Program in the 1950s and 1960s. Other countries have developed or are suspected to have developed VEE as a biological weapon.

The infective dose of VEE is 10 to 100 organisms, which is one of the reasons that VEE is considered a potential bioterrorism agent.

Venezuelan equine encephalitis could theoretically be produced in large amounts and intentionally disseminated as a highly infectious aerosol. It could be spread by the dissemination of infected mosquitoes.

Epidemiology

Alphaviruses primarily infect birds, rodents, equines, and primates. Horses develop a fatal encephalitis after infection with WEE, EEE, or VEE.

Alphaviruses are amplified in reservoir hosts and then transmitted to human by mosquitoes. There is no person-to-person transmission.

Hawaii has mosquito species that can potentially transmit alphaviruses.

Aerosol transmission within a laboratory setting has occurred, and has been responsible for laboratory-associated outbreaks of alphavirus infections.

Alphaviruses are limited in their geographic spread by the range of their mosquito vectors. Equine epizootics usually precede human outbreaks by 1 to 2 weeks. A bioterrorism attack with an alphavirus would most likely cause simultaneous disease outbreaks in humans and horses. A reliable method for determining the likelihood of a bioterrorism event would be the presence of alphavirus encephalitis outside of its natural geographic range.

VEE, WEE, and EEE can produce asymptomatic infection, a non-specific febrile illness, or encephalitis.

The diagnosis of alphavirus encephalitis is usually made by analysis of epidemiologic data, clinical presentation, and serologic studies. Viral isolation from brain, blood, and cerebrospinal fluid is available. Polymerase chain reaction (PCR) diagnostic methods are available in research centers.

Venezuelan Equine Encephalitis (VEE)

Venezuelan equine encephalitis is a cause of epizootic outbreaks of encephalitis in horses in South America.

The mosquito vectors are *Culex, Aedes, Mansonia, Psorophora,* and *Deinocerites spp.* Rodents are the virus reservoir. VEE strains capable of infecting humans and horses are initially amplified in horses. Equine disease precedes human disease by 1 to 2 weeks. The outbreak begins in a tropical forest during the rainy season, and continues until all horses are dead or immune.

During a VEE outbreak, human attack rates range from 10% to 60%. The mortality rate is about 0.6%.

The incubation period is 1 to 6 days. The disease begins as an influenza-like illness with malaise, chills, fever, headache, photophobia, myalgia, nausea, vomiting, cough, sore throat, and diarrhea that lasts for 2 to 5 days. A post-infectious fatigue syndrome lasting about 2 weeks may follow the acute illness. Physical signs during the acute illness include conjunctival injection, an erythematous pharynx, and muscle tenderness. Encephalitis is rare. Only 4% of children and 1% of adults will develop neurologic disease. If encephalitis occurs, it will be fatal in 35% of children

and 10% of adults. Altered levels of consciousness, disorientation, nuchal rigidity, seizures, paralysis, personality changes, ataxia, and coma are signs of encephalitis.

The white blood cell count will initially show leukopenia. There may be a mild thrombocytopenia. Liver enzymes may be elevated. The cerebrospinal fluid (CSF) examination is characteristic of "aseptic meningitis", and will demonstrate a modest pleocytosis of several hundred lymphocytes. There may be an elevation of the CSF pressure, and a modest increase in the CSF protein value.

VEE should be suspected in febrile individuals with flu-like symptoms who live in enzootic areas, or where epizootic disease has occurred regularly. Prior evidence of VEE infection in equine populations preceding human disease by 1 to 2 weeks should increase the level of awareness of VEE.

Venezuelan equine encephalitis infection during pregnancy may cause encephalitis in the fetus, placental damage, abortion, or severe congenital neuroanatomic anomalies.

The differential diagnosis of VEE in Hawaii includes influenza, hepatitis, leptospirosis, murine typhus, and other causes of "aseptic meningoencephalitis".

A positive IgM ELISA for VEE in serum or CSF can establish a serodiagnosis of VEE in a sample taken 5 to 7 days after onset of illness. Acute and convalescent IgG serology for VEE demonstrating a fourfold rise in antibody titer can also establish the diagnosis of VEE.

Venezuelan equine encephalitis can be isolated from nasopharyngeal swabs, blood, CSF, or brain tissue inoculated into cell cultures or suckling mice. VEE culture should only be attempted in biosafety level -3 laboratories.

There is no specific treatment for VEE. Supportive care may include analgesics for pain, anticonvulsants for seizures, fluid and electrolyte management, proper oxygenation, and assurance of adequate ventilation, proper nutrition, and prevention and treatment of hospital-acquired infections.

Mosquitoes should be kept from biting the patient. Patients should be placed in a screened room or quarters treated with a residual insecticide for five days or until the patient is afebrile. Humans can infect mosquitoes for at least 72 hours after onset of illness.

Patient isolation or quarantine is not indicated. Standard precautions are adequate. The virus can be destroyed by heat (80°C for 30 minutes) and standard disinfectants.

No pre-exposure or post-exposure immunoprophylaxis or chemoprophylaxis exists.

Preventive measures against VEE include mosquito control and a licensed equine vaccination with a live attenuated VEE strain (TC-83). This same strain can be used as an Investigative New Drug (IND) vaccine for laboratory workers exposed to VEE. A formalin-inactivated killed vaccine (C-84) is anther IND vaccine that is used as a booster vaccine to increase antibody titers in an individual who has received TC-83 in the past.

Western Equine Encephalitis (WEE)

Western equine encephalitis is a summertime disease occurring in humans and horses in the United States and Canada west of the Mississippi River. The vectors are *Culex tarsalis* and *Culiseta melanura*. Birds are the reservoir.

Western equine encephalitis is uncommon. Risk factors include rural residence, farming, and male gender. During a WEE epidemic, seroconversion is extremely high, but in the adult population there is only a 1:1,000 case to infection ratio. Encephalitis is more common in infants, with a case to infection ratio of almost 1:1. WEE is less neurovirulent than EEE. Attack rates for neurologic disease during a WEE outbreak ranges from 23 to 172/100,000 cases, with a case-fatality rate of approximately10%.

The incubation period is 5 to 10 days. Prodrome and neurologic manifestations are similar to VEE, but the neurologic manifestations are more frequent. A complete blood count often reveals a leukocytosis. CSF exam often reveals lymphocyte counts of 50 to 500 cells/mm^3. Serious residual neurologic complications follow WEE in 30% of infants. Parkinsonism is a complication of WEE in adults.

Western equine encephalitis should be suspected in endemic areas during the summer in patients having acute onset febrile illness with neurologic symptoms. Most cases can be diagnosed by paired sera or with specific IgM ELISA tests. The virus may be isolated from the brain post mortem.

There is no specific therapy, and supportive care as discussed with VEE is very important. Standard precautions are adequate for infection control purposes.

There is no indication for isolation or quarantine. General preventive measures include mosquito control and vaccination of horses.

Eastern Equine Encephalitis (EEE)

Eastern equine encephalitis is rare. It occurs in focal endemic areas in the Atlantic and Gulf Coast states. The primary insect vector is *Culiseta melanura*. This mosquito does not feed on humans, but transmits the virus to passerine birds that inhabit swampy and forested areas and serve as the reservoir for EEE. This mosquito overwinters as a larva in organic floating rootmat systems in the eastern United States. EEE virus must then become established in *Aedes* or possibly *Coquillettidia* mosquitoes that can then transmit the virus to horses and humans. There is no prolonged viremia in horses so that horses do not serve as a reservoir for EEE.

Although rare, outbreaks of EEE are important because the disease is severe. The case fatality rate ranges from 50% to 70%. Attack rates are highest among young children and the elderly. Survivors generally have significant neurologic complications such as seizures, paralysis, personality changes, and intellectual impairment.

The encephalitis presentation is similar to VEE and WEE. Malaise, fever, and vomiting are the initial symptoms that rapidly progress to altered levels of consciousness, disorientation, nuchal rigidity, seizures, paralysis, and coma. CSF findings reveal a lymphocyte predominant pleocytosis of 600 to 2000 cells/mm^3 and an elevated CSF protein of 100 to 150 mg/dL.

Diagnosis is established by acute and convalescent serology, by complement fixation, hemagglutination inhibition, or neutralization assays. Specific IgM ELISA for EEE can also establish the diagnosis. The virus can be isolated from the serum during the prodrome stage and from the brain post mortem.

Treatment, prevention, and infection control are similar to those against WEE.

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Chapter 10

Viral Hemorrhagic Fevers

Definition

The viral hemorrhagic fevers (VHFs) are a diverse group of illnesses caused by RNA viruses from four viral families:

- **Arenaviridae**
  Argentine hemorrhagic fever (Junin virus)
  Bolivian hemorrhagic fever (Machupo virus)
  Brazilian hemorrhagic fever (Guanarito virus)
  Venezuelan hemorrhagic fever (Sabia virus)
  Lassa fever virus

- **Bunyaviridae**
  Congo-Crimean hemorrhagic fever (CCHF)
  Rift Valley fever virus (RVF)
  Hantavirus

- **Filoviridae**
  Ebola virus
  Marburg virus

- **Flaviviridae**
  Dengue virus
  Yellow fever virus

These viruses have the potential for aerosol dissemination or weaponization, or likelihood for confusion with similar agents that might be weaponized.

Epidemiology

Arenaviridae are transmitted from their rodent reservoirs to humans by the inhalation of dusts contaminated with rodent excreta. Most are endemic to South America. Lassa fever is endemic and epidemic in Nigeria, Sierra Leone, Guinea, and Liberia. Lassa fever can be transmitted by close person-to-person contact.

Congo-Crimean hemorrhagic fever is a tick-borne disease that occurs in the Crimea and in parts of Africa, Europe, and Asia. It can be spread by contact with infected animals and in health care settings.

Rift Valley fever virus is a mosquito-borne disease that occurs in sub-Saharan Africa. Neither person-to-person nor nosocomial transmission has been reported.

The hantaviruses are rodent-borne viruses with a wide geographic distribution. Hantaan and Seoul viruses are the cause of Hemorrhagic Fever with Renal Syndrome (HFRS) in Korea, China, Japan, the Russian Far East, Bosnia, Serbia, and Greece. The Puumala virus causes a milder form of HFRS in northern Europe called Nephropathia epidemica. Hantavirus Pulmonary Syndrome is associated with the Sin Nombre, Bayou, and Black Creek Canal viruses in North America. Hantaviruses are transmitted to humans by the inhalation of dusts contaminated with rodent excreta.

Ebola hemorrhagic fever outbreaks have occurred in the Sudan and Zaire in 1976, Sudan in 1979, Kitwit, Zaire in 1995, and in Gabon and the Ivory Coast. Mortality from Ebola virus disease is 50% to 90%. The first Marburg virus outbreak occurred in Marburg, Germany and Yugoslavia following exposure of individuals to African green monkeys. Five additional outbreaks have been identified in Africa. Filoviruses are transmitted from human to human by direct contact with infected blood, secretions, organs, or semen. The natural reservoir of the filoviruses is unknown.

Yellow fever and dengue are mosquito-borne viral diseases. Tick-borne flaviruses include the agents of Kyanasur Forest disease in India, and Omsk hemorrhagic fever in Siberia.

The viral hemorrhagic fevers agents are infectious by aerosol in the laboratory except for dengue virus. Many of these agents are highly lethal.

Clinical Features

The target organ in VHF is the microvascular system. There is increased vascular permeability leading to edema. There is also frank vascular disruption leading to hemorrhage. Blood pressure is reduced, and in severe cases shock develops. The microvascular or

endovascular pathology produces a wide variety of multisystem abnormalities.

Common symptoms associated with viral hemorrhagic fevers include:

- The sudden onset of fever, myalgia, headache, vomiting, diarrhea, prostration and hyperesthesia.
- Abdominal pain can be severe, and in some cases may masquerade as an acute surgical abdomen.
- Physical findings may include conjunctival suffusion, facial flushing, periorbital edema, petechial hemorrhages, muscle tenderness, and hypotension.
- Severe cases feature some combination of shock, generalized mucous membrane hemorrhage, pulmonary edema, coagulopathy, abnormal liver enzyme tests, renal insufficiency, and neurologic abnormalities.
- Jaundice, abnormal liver enzymes, and fever are seen with RVF, CCHF, Marburg and Ebola hemorrhagic fevers, and yellow fever.
- Retinal vasculitis is seen in 10% of cases of RVF.
- A biphasic illness with pulmonary disease and neurologic manifestations are common with Kyanasur Forest disease and Omsk hemorrhagic fever.
- Lassa fever has hearing loss, and severe peripheral edema due to a capillary leak syndrome; hemorrhage is uncommon. A maculopapular rash may be seen in light skinned individuals.
- Hemorrhage is common with the South American aernavirus infections. Neurologic symptoms are common. Thrombocytopenia is the rule. Person-to-person transmission is rare.
- Congo-Crimean hemorrhagic fever has severe hemorrhage and nosocomial transmission.
- Disseminated intravascular coagulation is seen early with HFRS, CCHF, and the filovirus infections.
- Renal failure is prominent in Hemorrhagic Fever with Renal Syndrome. Pulmonary involvement is characteristic of Hantavirus Pulmonary Syndrome. The liver is primarily involved in yellow fever.
- Hemoconcentration is commonly seen in HFRS and dengue hemorrhagic fever.

Diagnosis

The diagnosis of natural VHF should be considered when a patient presents with the proper travel history and a severe febrile illness with evidence of vascular involvement. Symptoms and signs of vascular involvement include postural hypotension, petechial hemorrhages, coagulopathy, flushing of the face and chest, and non-dependent edema. Headache, myalgias, photophobia, pharyngitis, cough, nausea, vomiting, diarrhea, constipation, abdominal pain, hyperesthesia, dizziness, confusion, and tremor may be present in some cases.

Thrombocytopenia is a good screening test for VHF (except for Lassa fever). Leukopenia is also common, but is not present in Lassa fever, Hantaan virus infection, and severe CCHF cases. Proteinuria and/or hematuria are common especially in HFRS and the South American hemorrhagic fevers.

The differential diagnosis of possible VHF in Hawaii includes leptospirosis, murine typhus, fulminant hepatitis A, B, or C disease, meningococcemia, typhoid fever, non-typhoidal salmonellosis, shigellosis, dengue fever, and malaria. Non-infectious diseases that can mimic VHF include acute leukemia, systemic lupus erythematosus, idiopathic or thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation from causes other than VHF.

Definitive diagnosis requires specific virologic diagnosis based upon serologic tests. Rapid enzyme immunoassays can detect viral antigens in acute sera from patients with Argentine hemorrhagic fever, Lassa fever, RVF, CCHF, and yellow fever, HFRS, and Marburg virus infection. Viral isolation requires precautions in the collection, handling, shipping, and processing of blood, body fluids, and tissues. BSL-4 laboratories are required for viral isolation. Viral isolation may take several days to weeks.

Clinical Management

Meticulous supportive care is essential. Almost all patients will require intensive care management. Vigorous fluid resuscitation of hypotensive patients might result in pulmonary edema from pulmonary capillary leakage. Vasopressor agents may be needed for shock to maintain an adequate perfusion pressure to vital organs. Clinical bleeding due to a systemic coagulopathy may be present and require treatment.

Ribavirin is available via compassionate use protocols for treatment of Lassa fever, HFRS, CCHF, and RVF. Ribavirin has poor *in vitro* and *in vivo* activity against the filoviruses and the flaviviruses.

Prevention

The only licensed vaccine available for any of the hemorrhagic fever viruses is yellow fever vaccine, which is mandatory for travelers to endemic areas of Africa and South America. Investigational vaccines are being tested against Argentine hemorrhagic fever and HFRS.

Close personal contacts or medical personnel exposed to blood, body fluids, secretions, or excretions from a patient with suspected VHF should immediately wash the affected skin surfaces with soap and water. Mucous membranes should be irrigated with copious amounts of water or saline. They should be monitored for symptoms, fever and other signs of VHF during the established incubation period.

Contacts of Ebola and Marburg virus cases, or individuals with exposure in laboratories should be placed under health surveillance for 21 days after their last exposure to infection. If the contacts become feverish, they should undergo risk assessment and may be admitted to strict isolation pending the results of diagnostic tests.

A Department of Defense compassionate use protocol exists for prophylactic administration of oral ribavirin to high risk contacts (direct exposure to body fluids) of CCHF patients. A similar post-exposure strategy has been suggested for high risk contacts of Lassa fever patients.

Public Health Concerns

Any case of a viral hemorrhagic fever that is diagnosed in Hawaii must be immediately reported to the Department of Health.

With the exception of HFRS, dengue virus, yellow fever, and RVF, the VHF have significant viremia that can be transmitted through blood and body fluids to health care workers. Special caution must be exercised in handling sharps, needles, and other potential sources of parenteral exposure. Strict adherence to standard precautions will prevent nosocomial transmission of most VHF.

Lassa fever, CCHF, Ebola and Marburg viruses may be particularly prone to aerosol nosocomial spread. The patient should be managed in a private room. An adjoining anteroom for putting on and removing protective barriers, storage of supplies, and decontamination of recirculated air under negative pressure is advised for patients with significant cough, hemorrhage, or diarrhea. All persons entering the room should wear gloves and gowns (contact isolation). In addition, face shields or surgical masks and eye protection are indicated for those coming within three feet of the patient. Respiratory protection should be upgraded to airborne isolation, including the use of a fit-tested HEPA filtered respirator, a battery powered air purifying respirator, or a positive pressure supplied air respirator, if patients with the above conditions present with a prominent cough, vomiting, diarrhea, or hemorrhage. Caution should be exercised in evaluating and treating the patient with suspected VHF. Overreaction on the part of health care providers is inappropriate and detrimental to both patient and staff. However, it is prudent to provide rigorous isolation measures as feasible.

Laboratory specimens should be double-bagged, and the exterior of the outer bag decontaminated prior to transport to the laboratory. Excreta and other contaminated materials should be autoclaved or decontaminated by the liberal application of hypochlorite or phenolic disinfectants. Clinical laboratory personnel are also at risk for exposure, and should employ a biosafety cabinet and barrier precautions when handling specimens.

No carrier state has been observed for any VHF, but excretion of virus in urine (e.g. Lassa fever) or semen (e.g. Argentine hemorrhagic fever) may occur during convalescence. Should the patient die, there should be minimal handling of the body, with sealing of the corpse in leak-proof material for prompt burial or cremation.

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